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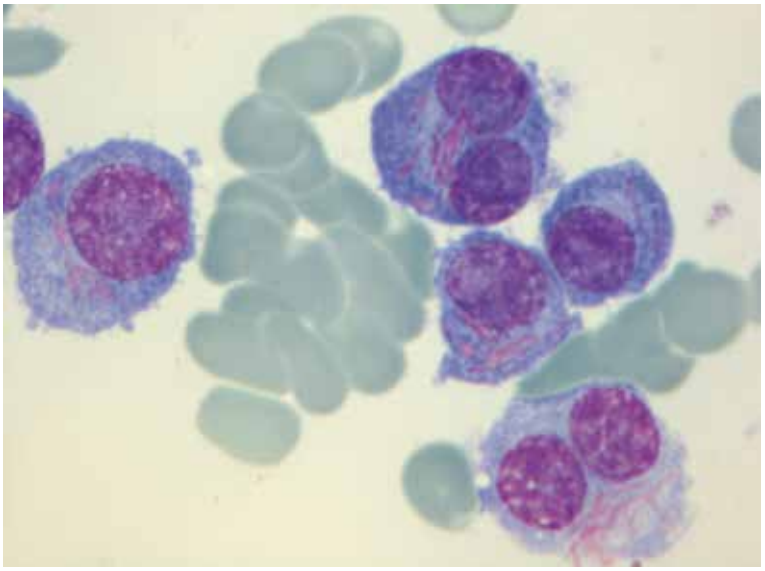

"An abnormal blood smear: what is your diagnosis"

Prolonged QT interval and intoxications
•
New-onset diabetes mellitus in kidney transplantation
•
Diagnosis and treatment of spondylodiscitis
•
Predictors of colorectal neoplasia after polypectomy
•
Bridging anticoagulation and risk factors for bleeding
•
Decision making in elderly lymphoma patients
•
Antibiotic treatment of community-acquired pneumonia

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The Journal of Medicine

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EDITORIAL

The Netherlands Journal of Medicine entering a next era

M. Levi

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Five years ago the editorship of *the Netherlands Journal of Medicine* moved from Nijmegen to Amsterdam.[1] The year 2014 will mark the transfer of the editorial team of *the Netherlands Journal of Medicine* to Rotterdam and the responsibility will pass to Dr. Paul van Daele of the Erasmus Medical Center in Rotterdam. When we took over the Journal in Amsterdam in 2009 we set ourselves a number of goals.

In the first place the aim of the Journal is to keep all internists informed of major developments within the broad discipline of Internal Medicine. To achieve that goal we tried to increase the number of high-quality review manuscripts to at least 3-4 per issue. Indeed, this journal category attracted a lot of attention as illustrated by the large number of downloads and a relatively high citation rate.[2] Also some of our recent review articles were very highly cited and contributed for a major part to the visibility of the Journal.[3-6] A special subcategory is guidelines, which is also a well-read type of article with a very high profile.[7-11] Simultaneously, the relative value of guidelines for clinical medicine was critically appraised.[12]

In the original article section we tried to publish papers with novel findings or great relevance for daily clinical practice. Some of these papers indeed attracted a lot of attention.[13] Other papers touched controversial issues and were also subject to debate and discussion.[14,15]

Our second aim was to further foster our role as an international journal. Obviously, the origin and name of the Journal may suggest a typical Dutch scope, but this is only true to a limited extent. Indeed, over the last five years our international submissions increased from 30% to 68%, with a more than fourfold increase in submissions.[16] The largest increase in submissions was seen from North America and from non-Western countries. Nevertheless, we did publish papers with a typical Dutch background, especially when we thought they could be of interest for an international readership as well.[17,18]

A third aim of *the Netherlands Journal of Medicine* is to provide a platform for our residents to publish short papers on interesting patients. Indeed, publication of one or two papers in a scientific journal is a requirement for our residents to obtain their license and although many of them participate in a research project, for some of the residents publication of an interesting or unusual patient or series of patients is an important means to fulfil this obligation.[19] Our case report and particularly our popular photo quiz sections contain these contributions. Although we do not exactly know how often these short articles are written by residents, we have the impression that many of our residents have taken the opportunity to publish in *the Netherlands Journal of Medicine* in recent years.

Lastly, our aim was to improve the impact factor of the Journal. This is obviously not a goal in itself, but we and others have noted that an increase in the impact factor leads to more and better submissions, which will result in a selection of even better papers for publication that eventually will further increase the impact factor. Over the last five years the impact factor of the Journal has steadily risen from 1.2 to almost 2.8.[2] This is not trivial as the vast majority of general medical journals have an impact factor of less than 2 and with its current impact factor *the Netherlands Journal of Medicine* belongs to the top-25 of international general medical journals. An increase in submissions and a fixed space for publication, however, invariably leads to a lower acceptance rate. Indeed, we have had to disappoint an increasing number of authors in recent years but on the positive side this did not stop many of them from continuing to submit papers to our Journal.

We are very grateful for the help we have had in the last five years in producing and improving *the Netherlands Journal of Medicine*. A great part of the success was achieved by the enthusiastic and energetic support of our large group of junior associate editors. This group consisted of residents in training for Internal Medicine who had research

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experience and obtained their PhD before they started their specialisation. They were responsible for the majority of the review work and the ensuing editorial decisions, and each of them handled many articles per year. The senior associate editors and editorial board were very helpful in commissioning and judging the many review articles that we published in recent years. Lastly, but importantly, the highly professional assistance of our publisher is gratefully acknowledged.

We are confident that *the Netherlands Journal of Medicine* will remain a high-quality monthly journal that is of value for every specialist interested in Internal Medicine in the world. We wish the new editors, headed by Paul van Daele, a lot of success and we hope that they will receive the same support and positive spirit from the scientific-medical community in the Netherlands and abroad that we have met during our editorship.

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REVIEW

Management of prolonged QT interval and torsades de pointes in the intoxicated patient

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ABSTRACT

Many drugs can significantly influence cardiac repolarisation causing an increased duration of this repolarisation phase, challenging the repolarisation reserve. This may set the stage for life-threatening ventricular arrhythmias such as torsades de pointes (TdP). TdP generally occurs in conjunction with a prolonged QT interval (QT) on the electrocardiogram. The Dutch Poisons Information Centre (NVIC) often receives information requests about drugs that can influence the QT already at therapeutic dosages. Drug-induced QT prolongation is dose dependent and hence can be particularly pronounced in overdose situations. Also, additional risk factors for the development of life-threatening arrhythmias are often present in intoxicated patients.

This review focuses on identification and management of drug-intoxicated patients who are at risk for a reduction in their repolarisation reserve, measured by their QT interval. The QT interval is strongly dependent on heart rate, which has led to the introduction of different methods to adjust the QT interval, i.e. the QTc. Bazett's formula, which has been used for decades, lacks accuracy concerning QTc calculation at higher and lower heart rates, situations often relevant when dealing with intoxicated patients. Additionally, we highlight drugs with QT-prolonging potential that are commonly associated with an overdose setting in the Netherlands. Finally, standard treatment options specifically pointed toward the intoxicated patient at risk of QT prolongation and TdP will be discussed.

KEYWORDS

Intoxication, Torsades de Pointes, treatment, QT prolongation, QTc and Bazett's formula

INTRODUCTION

In drug overdose, a prolonged QT interval (QT) on the electrocardiogram (ECG) is an important diagnostic tool to assess whether an individual is at risk of developing life-threatening ventricular arrhythmias.[1,2] The QT can be measured on the standard ECG from the beginning of the QRS complex to the end of the T wave, thus representing the complete ventricular depolarisation and repolarisation phase.[3] At the cellular level, the electrocardiographically prolonged QT interval is primarily based on a reduction of net repolarising ion channel currents resulting in a prolonged repolarisation. This, in turn, sets the stage for oscillations of the membrane potential, which can give rise to additional depolarisations during the repolarisation phase, known as early afterdepolarisations (EADs).[4] If the amplitude of these EADs reaches a critical threshold, and occurs in a sufficiently large myocardial area, ectopic ventricular beats can ensue. The most common ventricular arrhythmia that can arise under these circumstances of a prolonged QT interval is torsades de pointes (TdP).[5]

TdP is defined as a polymorphic ventricular tachycardia exhibiting a 'twisting of the points' pattern around the isoelectric line of the ECG.[6,7] Generally, TdP episodes are self-terminating but can also degenerate into ventricular fibrillation and thus sudden cardiac death.

The pathophysiological mechanisms underlying and favouring the development of TdP are complex and not completely unravelled. It has been shown that several disturbances in different flows of ions can be involved. Na^+ (I_{Na}), K^+ (I_{Ks}, I_{Kr}) and Ca^{2+} (I_{Ca}) currents have all been implicated.[3,8-11] Interference of ion channels that mediate these currents, either through gain or loss of function, or regulation, has been shown to prolong the duration of the repolarisation phase.[12]

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In the majority of cases, the mechanism by which drugs can cause a prolonged QT is due to the interaction with the human Ether-a-go-go Related Gene (hERG) subunit of the rapidly activated delayed rectifier K^+ channel. This interaction blocks the inward K^+ current (I_{Kr}), prolonging the repolarisation phase and thus increasing the likelihood of EADs.[13,14]

This review focuses on the identification, individual risk stratification and management of intoxicated patients (patients who have been misdosed or overdosed, intentionally or unintentionally). Depending on the situation, this subset of patients can be at particular risk for QT prolongation and subsequent malignant arrhythmias such as TdP. We review several methods recommended to determine the rate-corrected QT (QTc) for different heart rates. Additionally, we highlight which potential QT-prolonging drugs are commonly associated with an overdose setting in the Netherlands. Finally, the current advocated treatment of QT prolongation and TdP in intoxicated patients will be outlined.

RISK FACTORS AND DRUGS THAT CAN AFFECT THE QT INTERVAL

Risk factors

A number of risk factors have been described that raise the likelihood of QT prolongation, increasing the chance to develop life-threatening ventricular arrhythmias.

The most common acquired pathological conditions that are associated with QT prolongation are electrolyte disturbances. Particularly hypokalaemia[1,2,15] hypomagnesaemia[2,16-18] and hypocalcaemia[15,19] can alter cellular ionic homeostasis and thus cause electrical dysbalance and promote arrhythmias.

Moreover, a number of different pathological conditions may strongly influence cardiac repolarisation and QT prolongation, i.e., bradycardia, left ventricular hypertrophy, congestive heart failure, cardiomyopathies, myocardial ischaemia and hypertension.[20]

Additionally, a very important risk factor for the development of QT prolongation is the genetic background. This genetic influence can range from an increased susceptibility to develop prolonged QT in response to medication (often polygenetic and dormant),[21,22] to the relatively rare monogenetic types of congenital long-QT syndromes.[23-25]

Other contributing factors are female gender,[26,27] and increasing age.[26,28,29]

Drugs associated with prolonged QT

Many different drugs can cause QT prolongation, some already at regular therapeutic dosages and others particularly in an overdose setting. There are several sources available that list drugs that are associated with prolonged QT. A drug list often used in literature is www.crediblemeds.org (previously www.torsades.org). This online inventory of drugs with potential QT-prolonging properties places drugs in three different risk categories for TdP. Currently 136 different drugs are listed on this website.

To give insight into which drugs are commonly associated with intoxications, a ranking was made of the number of information requests concerning these types of drugs to the Dutch Poisons Information Centre in 2012 (*table 1*). Unfortunately, European data are not available; nevertheless, we expect that the drugs summarised in *table 1* reflect the European situation.

MEASURING THE QT INTERVAL

QT interval

A number of manual and automated approaches to measure the QT interval have been described in the literature. Nevertheless, some pitfalls in determining the 'correct' QT interval remain.

Most experts agree that computerised measurements of QT and corrections for heart rate (QTc) are not sufficiently accurate.[30-33] Manual determination of the QT also has inherent shortcomings, i.e., identifying the onset of the Q wave, and especially the end of the T wave, may be subject to considerable misinterpretation and intra- or inter-observer variability.[33-36] Postuma *et al.* confirmed this variability, yet showed that with clear

Table 1. *Top 10 information requests at the Dutch Poisons Information Centre regarding intoxications with QT-prolonging drugs*

Rank	Drug (TdP risk grade)*	# Information requests in 2012
1	Quetiapine (2)	939
2	Citalopram (1)	387
3	Promethazine (2)	374
4	Venlafaxine (2)	337
5	Mirtazapine (2)	312
6	Paroxetine (3)	263
7	Olanzapine (2)	260
8	Fluoxetine (3)	229
9	Risperidone (2)	208
10	Sertraline (3)	195

***Risk grades as allocated by www.crediblemeds.org. (1) Risk for TdP: substantial evidence supports the conclusion that these drugs, at therapeutic levels, can prolong the QT interval and can have a risk of TdP in some patients. (2) Possible risk for TdP: substantial evidence supports the conclusion that these drugs, at therapeutic levels, can cause QT prolongation but there is insufficient evidence at this time that they have a risk of causing TdP. (3) Conditional risk for TdP: substantial evidence supports the conclusion that these drugs can prolong QT and therefore have a risk of TdP, but only under certain known conditions (e.g. excessive dose, drug interaction, etc.).**

instructions the QT interval can be calculated manually in a very accurate way (*figure 1A, C*).[37] *Figure 1* provides two examples of manual approaches that have proven to give reliable and reproducible measurements of the QT interval; with some practice they take only 1-2 minutes (*figures 1A* and *1B*). A third and quick option in cases of emergency is suggested in Goldfrank's toxicological emergencies, where only the bipolar limb lead that best shows the end of the T wave is measured and averaged over 3 to 5 beats.[11]

QT interval correction for heart rate

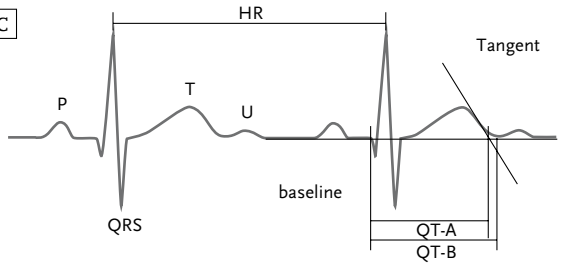
The QT interval importantly depends on heart rate. The interval is prolonged at slower heart rates and shortens as the heart rate increases. Already in the 1920s, Henry Cuthbert Bazett developed a formula to correct for this heart rate dependence and introduced what is known as the corrected QT (QTc).[38] Yet, it is well known that this formula tends to overcorrect at a faster heart rate while undercorrecting at low heart rates.[39-48] This leads to a tendency to be too conservative at high heart rates, while under-correcting at low heart rates.

Figure 1. *Two methods of manual QT interval determination*

A **Method 1**
- Measurement taken from the Q-wave to the intersection of the tangent to the steepest slope of the last limb of the T-wave and the baseline
- Read lead II or V5 if lead II is unclear
- Take the mean of three measurements

B **Method 2**
- Measurement taken from the Q-wave to the point where the T-wave returns to the baseline
- QT measured in 6 leads total: 3 limb leads and 3 chest leads
- Take the median of the six individual leads

C



Examples of the manual measurement as recommended by A) Viskin et al. 2005 (36) and Postema et al. 2008 (37) or B) by Isbister & Page 2012. (57) C) Illustration of these two methods (adapted from Postema et al. 2008 (37) with permission of Elsevier).

Table 2. *Studies comparing different heart rate correction formulae*

Subjects studied	# Patients	Range of HR (bpm)	Formulae tested	Recommended formulae	Method of uncorrected QT measurement	Reference
Healthy subjects	10 000	40-125	- Bazett, - Fridericia - Framingham - Hodges	**M:** HR < 100: Fridericia HR > 100: Hodges **F:** HR < 100 Hodges, HR > 100 Fredericia **All:** HR < 60 Fredericia HR > 60 Hodges	Automatic (an algorithm reporting the 'true' longest interval from multiple leads excluding clear outliers)	Luo *et al.* 2004
TdP patients	129	30-160	- Bazett - Isbister nomogram	**M:** n.s. **F**: n.s. **All**: Isbister nomogram	Median of six ECG leads	Chan *et al* 2007
Pacemaker candidates without significant heart disease	41	60-100	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram	**M**: n.s. **F**: n.s. **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2010
Drug intoxicated patients (with & without QT- prolonging properties)	541	30-150	- Bazett – Isbister nomogram	**M**: n.s. **F**: n.s. **All**: Isbister nomogram	Median of six ECG leads	Waring *et al.* 2010
L-QT patients (TdP versus non-TdP)	29	47-79	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram – Rautaharju	**M**: Hodges **F**: Hodges **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2012
Bundle branch block patients	71	60-100	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram – Rautaharju	**M**: n.s. **F**: n.s. **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2012
Dual-chamber device recipients with & without QT prolongation	123	52-100	- Bazett, - Fridericia - Sagie-Framingham - Hodges – Karjalainen nomogram	**M**: n.s. **F**: n.s. **All**: Hodges	Max QT in any of 12 leads	Chilakadis *et al.* 2010

bpm = beats per minute; F = female; HR = heart rate; M = male; n.s. = not specified; TdP = torsade de pointes.

This tendency to underestimate the QT interval at low heart rates is particularly treacherous as the risk of TdP increases when the heart rate decreases.[33,41,43,49,50] Nevertheless, to date Bazett's formula is routinely used in automated ECG measurement to determine the corrected QT interval (QTc) for heart rate. It should be noted that Bazett's formula adequately corrects for heart rates varying between 50 and 90 beats per minute (bmp).[11,51,52]

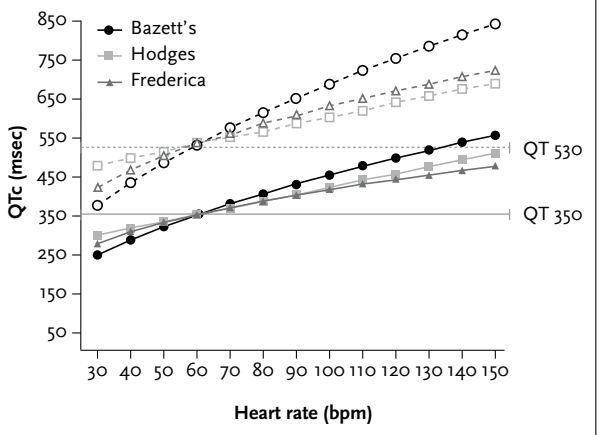
Trying to compensate for the shortcomings of Bazett's formula a number of alternative formulae have been introduced. Already in 2009 the American Heart Association, in conjunction with the Council of Clinical Cardiology and the Hearth Rhythm Society, recommended to use a different formula which is less influenced by heart rate than the Bazett's formula.[53] No consensus about which formula is best has been reached, however. A literature search about this topic in the last decade shows that the formulae of Hodges and Fredericia and the QT nomogram of Isbister have been suggested as better alternatives for the Bazett's formula (*table 2*). These alternatives are especially valuable for patients with bradycardia or tachycardia, as differences ranging from 30 to >100 msec can be calculated depending on the heart rate of a patient (*figure 2*).

The largest study concerning this topic in the last decade was performed in 2004 and involved 10,000 ECG recordings.[46] The authors compared several correction formulae by calculating the dependence of the calculated QTc by these formulae on heart rate. Depending on sex and heart rate, they found different formulae superior to Bazett's formula (where the smallest correlation between heart rate and QTc was deemed best) (*table 2*). A potential confounding factor in this study is that the measurements were all performed automatically. Other studies in smaller patient groups and with manual ECG reading in patients, suffering from different heart conditions, confirmed that Hodges' formula and Fridericia's formula are superior to Bazett's formula.[42,3,54,55]

Isbister *et al.* decided not to use a direct correction for heart rate anymore, but to plot the heart rate against the uncorrected QT interval in a nomogram. The studies they performed using this approach have shown good specificity and sensitivity with regard to predicting patients at risk for developing TdP at various heart rates. The nomogram performed particularly well at low heart rates, making this method of heart rate correction particularly valuable in bradycardic situations when the risk for TdP is increased.[41,56,57]

In all, several strategies have been developed to measure the QT and to determine the QTc, a true golden standard has not generally been accepted, however. It therefore seems wise to follow the FDA's recommendation when analysing a patient who might be at risk for QT prolongation, which is to conduct a 'thorough QT study' in vulnerable patients (www.fda.gov). This means that an automated measurement with Bazett's correction for heart rate is not sufficient for patients at risk. The aforementioned approaches for QT and QTc measurements are all valuable tools for this thorough QT study.

Figure 2. *Comparison of three heart rate correcting formulae based on two values of uncorrected QT (350 ms and 530 ms)*



Bazett's correcting formula clearly gives higher values of QTc at faster heart rates and lower values with slower heart rates. These differences can lead to different risk stratifications.

RISK ASSESSMENT OF THE INTOXICATED PATIENT FOR TDP

The drugs listed on crediblemeds.org have all been implicated in QT prolongation to different degrees. High-risk drugs, such as erythromycin, methadone and haloperidol,[58,59] exhibit clear QT prolongation already at therapeutic concentrations. Drugs in a lower risk category, such as ciprofloxacin and fluconazole,[60-62] are likely to require additional risk factors, such as electrolyte disturbances, drug interactions, overdosage or bradycardia before resulting in QT prolongation and possible TdP. These risk factors are more likely to be present in the intoxicated patient (especially when a patient has been exposed to large amounts or combinations of drugs). Additionally, with virtually all QT-prolonging drugs the risk of prolonged QT times, and possible TdP, increases as a function of plasma drug concentration.[20] For citalopram, for instance, a clear relationship exists between the dose and the risk of QT prolongation and TdP.[63-65] However, for many drugs there is limited information on the risk for significant QT prolongation and TdP. Hence, cut-off values of acceptable

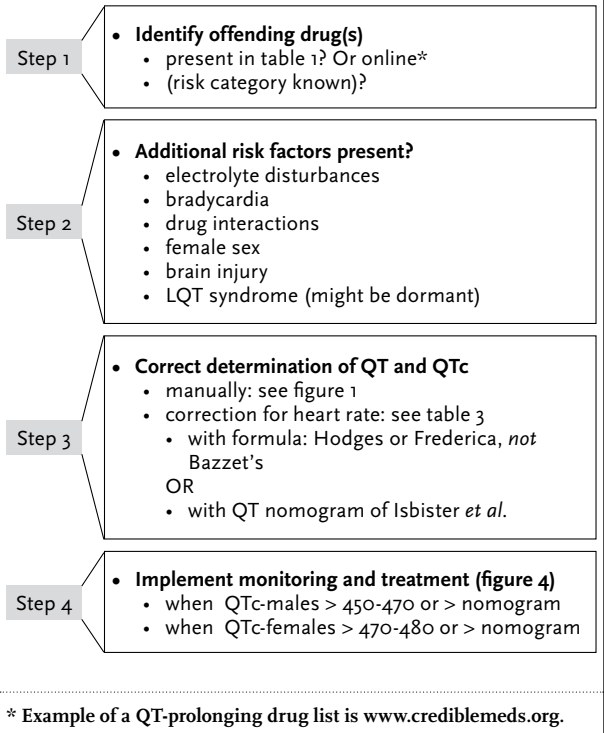
QTc times are used in the clinic, or the QT nomogram of Isbister *et al*. is used to determine the risk for TdP.
Depending on the source, a QTc >450 or 470 for males and >470 or 480 for females has been correlated to an increased risk of TdP and sudden death.[20,46,66,67] Additionally, data from congenital LQT studies and case reports and small series of patients with drug-induced TdP show that a QTc of >500 ms is associated with a 2- to 3- fold higher risk of TdP.[20,50,68-70]

TREATMENT OF THE INTOXICATED PATIENT WITH PROLONGED QTC

Correction of metabolic and electrolyte disturbances: particularly Mg^{2+} and K^+

Correction of electrolyte disturbances, bradycardia, acidaemia, hypotension and hypoxia is of the utmost importance (*figure 4*).[11,71,72]
Particularly hypomagnesaemia should be avoided as Mg^{2+} can suppress EADs. A Mg^{2+} level of 1-2 mMol/l is recommended (physiological levels: 0.7-1 mMol/l).
With regard to potassium levels it is recommended to maintain serum potassium between 4.5 and 5 mMol/l (physiological levels: 3.8-5.5 mMol/l) as this shortens the QT interval.[73,74]

Figure 3. *Recommended approach when encountering an intoxicated patient who might be at risk for QT prolongation and TdP*



*** Example of a QT-prolonging drug list is www.crediblemeds.org.**

Raising extra-cellular Na^+ and pH through bicarbonate treatment with drugs exhibiting Na^+ channel blocking properties

If the intoxication involves a drug with Na^+ channel blocking properties (e.g. tricyclic antidepressants, cocaine, IA and IC antiarrhythmics, or antipsychotic drugs) bicarbonate therapy can be used to lessen the degree of sodium channel blockade through increased extra-cellular sodium (*figure 4*).[11,75-78]

Saline appears to be less effective than sodium bicarbonate because some QRS-prolonging drugs are proposed to have a pH-dependent binding to the sodium channels, with less extensive binding at higher pH. The recommended pH level with bicarbonate treatment is between 7.50 and 7.55.[11,71] Using bicarbonate treatment with other drug exposures that do not affect Na^+ channels is contraindicated, due to the inherent the risk of inducing hypokalaemia with this treatment.

Replacing slow kinetic sodium block with fast kinetic antiarrhythmic agent lidocaine treatment with drugs exhibiting Na^+ channel blocking properties

Lidocaine is an antiarrhythmic drug that also blocks cardiac Na^+ channels. It therefore seems counterproductive to treat adverse events of other Na^+ blocking drugs with this drug. Yet the pharmacological properties of lidocaine are such that it displays rapid on and off kinetics.[79] To replace Na^+ blocking drugs that have slower kinetics with lidocaine has been shown to be beneficial for antipsychotics, class 1A and 1C antiarrhythmic drugs, sotalol and cocaine.[11,72] Additionally, in poisonings with tricyclic antidepressants (TCA) a beneficial effect of lidocaine has been reported, especially with TCAs displaying particularly slow on- and off-kinetics such as amitriptyline and nortriptyline.[71,80] The use of lidocaine in TCA poisoning is only recommended, however, when the cardiotoxicity is refractory to bicarbonate treatment.

Intravenous lipid emulsion (ILE) therapy or veno-arterial corporal membrane oxygenation (VA-ECMO) in non-responsive patients

If an intoxicated patient does not respond to the above-mentioned therapeutic measures, alternatives should be considered. Intravenous lipid emulsion (ILE) therapy can be considered, if the drug has lipophillic properties. If all fails veno-arterial corporal membrane oxygenation (VA-ECMO) should be considered. These treatments have been shown to be effective in several case series with severely intoxicated patients.[81-84] It is important to realise that in most intoxicated patients the support of VA-ECMO is usually needed for a short time only.

Treatment of torsades de pointes

A patient who progresses into TdP should be treated with 1-2 g (4-8 mmol) IV magnesium. Intravenous magnesium can suppress episodes of TdP without necessarily shortening QT. This effect can take place even if the levels of magnesium are normal.[85-87] However, serum Mg^{2+} should be monitored as magnesium toxicity can occur when concentrations exceed 3.0. mMol/l.[88] On the other hand, whenever episodes of TdP persist, it may be necessary to repeat these magnesium infusions.[89] If potassium repletion and magnesium supplementation is not sufficient to end the TdP, then cardiac pacing can be considered to increase the heart rate.[86,87] Transvenous atrial or ventricular pacing at rates >70 bpm are recommended.[90] Additionally, treatment with isoprenaline has been suggested in drug-induced QT prolongation and TdP, provided that ischaemia or hypo-hypertension are not present.[86,87] Again, VA-ECMO should be considered as a salvage therapy.[81,82]

CONCLUSION

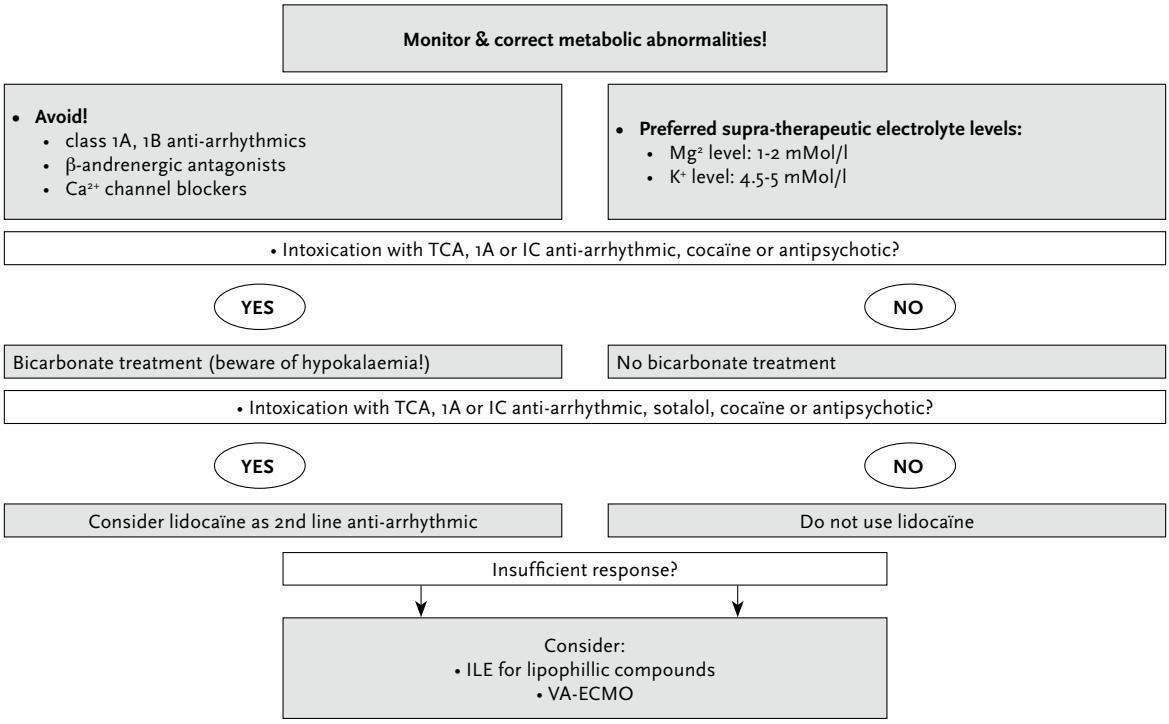
This review set out to give additional insights into the identification (*figure 3*) and management (*figure 4*) of the intoxicated patient who might be at risk for QT prolongation and possible TdP.

It has become clear that several factors need to be taken into account when doing this (*figure 3*). The imperative steps are firstly determining which QTc-prolonging drugs (or combinations) are involved, and secondly whether additional risk factors are present. Thirdly, the correct measurement of QT (*figure 1*) and QTc interval is imperative, especially for patients with bradycardia and tachycardia. For example; a bradycardic patient with a heart rate of 40 bpm and QT of 530 msec will have a QTc with Bazett's correction of 433 ms, Hodges correction 495 ms and Fredericia 464 ms (*figure 2*). Both Hodges and Fredericia, and also the nomogram of Isbister, will mark this patient as increased risk, while Bazett's correction would not.

The fourth step is to implement monitoring and treatment if necessary, focussing mostly on correcting acidaemia, hypotension, hypoxia, bradycardia and electrolyte disturbances.

In all, TdP is a life-threatening rhythm disturbance that can lead to sudden death. Identifying and managing intoxicated patients who are at risk for developing TdP is vital. Such patients need close monitoring in an intensive care facility until the intoxicating drug has been eliminated from the body and further risks eliminated. Using the correct method to determine the QTc and correction of electrolyte and metabolic disturbances are critical parts of this process.

Figure 4. *Recommended treatment approach for intoxicated patients with a prolonged QT*



ECMO = extra corporal membrane oxygenation; ILE = intravenous lipid emulsion; TCA = tricyclic antidepressants.

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REVIEW

Prevention and management of new-onset diabetes mellitus in kidney transplantation

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ABSTRACT

New-onset diabetes mellitus after transplantation (NODAT) is one of the complications that is increasingly occurring among kidney transplanted patients. It is associated with the risk of cardiovascular disease, graft failure and mortality. The risk of NODAT development increases with time from transplantation. Therefore, early detection and prompt action are essential in reducing the risk of NODAT and its complications. This paper aims to review the screening parameters, prevention and management strategies for NODAT in both pre- and post-transplantation conditions. The pre-transplant patient should be screened for diabetes and cardiometabolic risk factors. Blood glucose evaluation for the pre-transplantation period is important for early detection of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are highly associated with the incidence of NODAT. Post-kidney transplant patients should have periodical blood glucose monitoring with more frequent assessment in the initial phase. As early hyperglycaemia development is a strong predictor for NODAT, prompt intervention is needed. When NODAT develops, monitoring and control of blood glucose profile, lipid profile, microalbuminuria, diabetic complications and comorbid conditions is recommended. Immunosuppressive regimen modification may be considered as suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) guideline to reverse or to improve the diabetes after weighing the risk of rejection and other potential adverse effects. Strategies for modifying immunosuppressive agents include dose reduction, discontinuation, and selection of calcineurin inhibitor (CNI), anti-metabolite agents, mammalian target of rapamycin inhibitors (mTORi), belatacept and corticosteroids. Lifestyle modification and a conventional anti-diabetic approach, as in the type 2 diabetes mellitus guidelines, are also recommended in NODAT management.

KEYWORDS

New-onset diabetes mellitus, NODAT, post-kidney transplantation, prevention and management

INTRODUCTION

End-stage renal disease (ESRD) is a rising public health problem worldwide with a poor outcome and high cost. As reported by the United States Renal Data System (USRDS), the prevalence of ESRD in the United States has increased from 475,291 patients (1599 per million population) in 2005 to 593,086 patients (1752 per million population) in 2010.[1,2] In Australia, the prevalence of ESRD has also risen from 15,175 patients (746 per million population) in 2005 to 18,243 patients (843 per million population) in 2009.[2] ESRD patients require renal replacement therapy which consists of either dialysis or renal transplantation. Renal transplantation prolongs life, reduces morbidity, improves quality of life, enables social and medical rehabilitation and reduces the costs associated with the medical care of patients with ESRD.[3] Furthermore, the establishment of transplantation has been made possible by the introduction of immunosuppressant therapy.[4] In 2010, 16,843 kidney transplants were performed in patients aged 20 and older in the United States and 935 kidney transplants were performed among patients aged 19 and younger.[1]

Previous evidence demonstrates that post-transplant diabetes mellitus (PTDM),[5] now known as NODAT,[6] is an increasingly common complication of kidney transplantation. NODAT increases the risk of graft-related complications such as graft rejection, reduces graft function, graft loss and infection and subsequently reduces the survival of transplant recipients.[7,8] It is also a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients.[9] NODAT develops

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as a consequence of both impaired insulin production and increased insulin resistance. These complications consequently increase medical costs.[8,10]

Definition

PTDM is the term that was commonly used in the past to describe this disorder.[5] Clinically, PTDM was defined as the need for treatment with glucose-lowering agents post-transplantation for more than 30 days consecutively.[5] However, the definition of PTDM underestimated the prevalence of this disorder, particularly for patients with asymptomatic hyperglycaemia. Therefore, in 2003, the World Health Organisation (WHO) and American Diabetes Association (ADA) refined the term to NODAT.[6] NODAT is diagnosed by using three criteria. These criteria include symptoms of diabetes plus casual plasma glucose (PG) concentrations ≥200 mg/dl (11.1 mol/l) or fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l) or two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline[11] added haemoglobin A_{1C} (HbA_{1C}) as part of the screening criteria for NODAT.

Incidence of NODAT

The reported incidence of NODAT mostly ranged from 2-50%.[5,7,10,12-17] The wide variation in the incidence rate is due to differences in diagnostic criteria, observation periods, presence of risk factors and immunosuppressant therapy used in the studies. Data from USRDS showed that adult kidney transplant patients have a higher incidence of NODAT, 41% at 36 months as compared with 13% among paediatric patients.[1]

Risk factors of NODAT

Multiple risk factors have been identified in the development of NODAT. These include older age (≥40-45 years),[18-24] ethnicity,[7,21-25] family history of diabetes,[20,22,23] hepatitis C infection,[21-24] increasing human leukocyte antigen (HLA) mismatches,[7,16] obesity (body mass index, BMI ≥30kg/m²),[20-24] donor source,[26] acute rejection,[21,27] genetic factors[24,28,29] as well as the type of immunosuppressive agents used to prevent and/or treat rejection.[24,30-32] Some studies also suggested that cytomegalovirus infection,[15,22,23] autosomal dominant polycystic kidney disease,[23,27,33] number of metabolic syndrome components[13,21] and peritoneal dialysis[19,34] are risk factors of NODAT development. Further evidence is needed to evaluate the association between these risk factors and NODAT.

Evidence supports a strong link between immunosuppression regimens and the development of NODAT. Immunosuppression therapy has customarily constituted triple therapy with: (1) a calcineurin inhibitor (CNI) (cyclosporine (CsA) or tacrolimus (Tac)); (2) an anti-metabolite agent (azathioprine (AZA) or mycophenolate mofetil (MMF)); and (3) a corticosteroid. Corticosteroids and CNI have both been clearly documented as contributory to the onset of NODAT, whereas AZA and MMF do not seem to influence glucose control. The development of diabetes in transplant recipients receiving prednisolone has been reported to be as high as 46%.[35] Although both CsA and Tac have been associated with an increased risk for diabetes after transplantation, clinical studies indicate that the risk for developing diabetes was found to be up to five times higher with Tac at one year after kidney transplantation compared with CsA.[7,36-39] Sirolimus (Sir), a mammalian target of rapamycin inhibitors (mTORi), has been associated with higher incidence of NODAT especially when used in combination with CNI.[25] Whereas, the use of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody in induction therapy, was linked to the development of NODAT in a single centre, retrospective study.[32]

METHOD

A literature search was performed to identify published studies on prevention and management of NODAT in kidney transplant patients. The search strategy involved using Boolean connectors of the following terms: kidney transplantation, new-onset diabetes mellitus, post-transplantation, diabetes mellitus after transplantation, screening, management, prevention, and risk factors. The search was limited to full-text articles published in English between 1980 and 2013. The electronic databases searched included Scopus, ISI Web of Knowledge, PubMed, Science Direct, Springer Link, Proquest, Ebsco Host and Google Scholar. After excluding all irrelevant articles and duplicated citations, a total of 36 articles were included in the present review.

PREVENTION AND MANAGEMENT

Pre-transplantation screening and management

Before transplantation, all candidates are suggested to undergo a baseline evaluation including complete medical and family history, addressing both risk factors for diabetes[6,7,40] and other cardiometabolic risk factors such as hypertension, dyslipidaemia and smoking.[6,40] Periodical screening of FPG and/or OGTT are also recommended in evaluating the glucose metabolism status.[40,41] This screening helps to detect impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are highly associated with NODAT incidence. IFG is defined as FPG

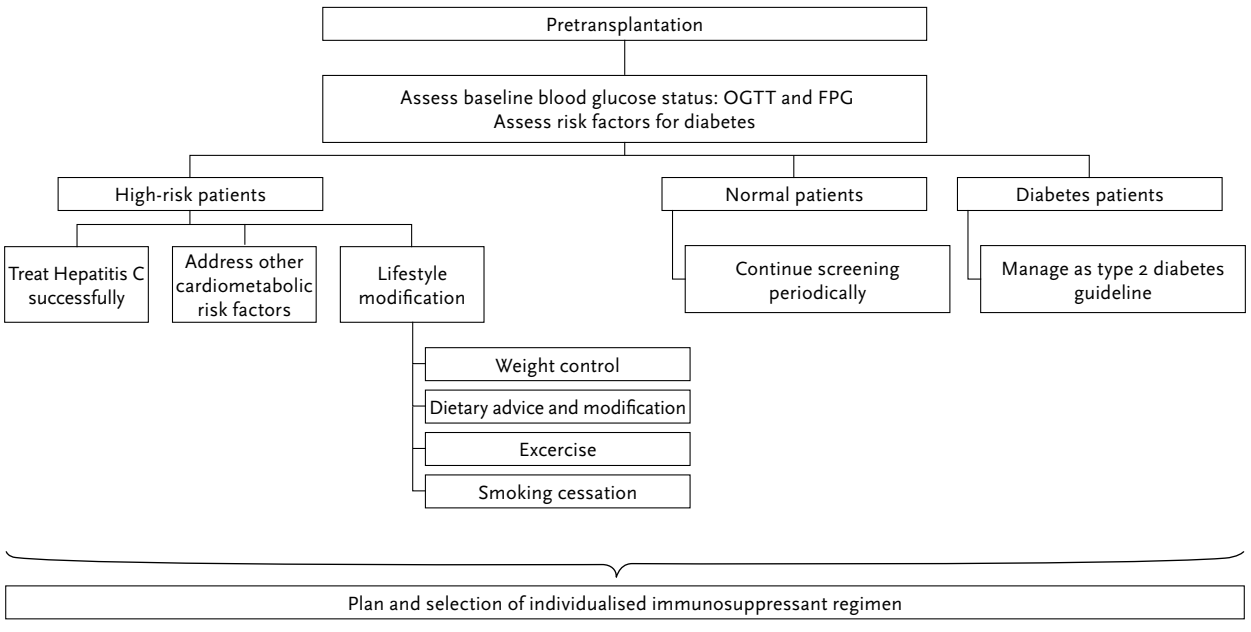
≥110 mg/dl (6.1 mmol/l) and <126 mg/dl (7 mmol/l). While assessing further with OGTT, IGT is defined as OGTT ≥140 mg/dl (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l).[40,42] However, optimal timing of pre-transplant screening has not been established.[40,43] HbA_{1C} is not recommended as part of the screening strategy owing to low sensitivity in ESRD patients.[40,41]

Patients at risk of NODAT should be counselled on the importance of lifestyle modification including weight control, diet, exercise and smoking cessation.[6,22,40] Overweight patients should achieve a weight reduction of at least 7% of the initial body weight.[43] Dietician referral may be needed to enhance the intervention. A low saturated fat and cholesterol and high complex carbohydrate and fibre diet is encouraged, especially in diabetic dyslipidaemia patients.[22] Physical activity of at least 150 minutes a week is recommended as a prevention strategy for NODAT.[22] Treatment of hepatitis C with interferon and sustained virological response prior to transplantation may reduce the risk of NODAT.[11,44] Studies have shown a lower incidence of NODAT in hepatitis C treated patients.[45,46] Other cardiometabolic risk factors such as dyslipidaemia and hypertension should be addressed accordingly.[43] After pre-transplant assessment, prospective tailoring of immunosuppressants may minimise the risk of NODAT.[6,15,40] *Figure 1* summarises the pre-transplant screening and management recommended by guidelines[6,11,40] and studies.[7,15,22,23,41-48]

Post-transplantation screening

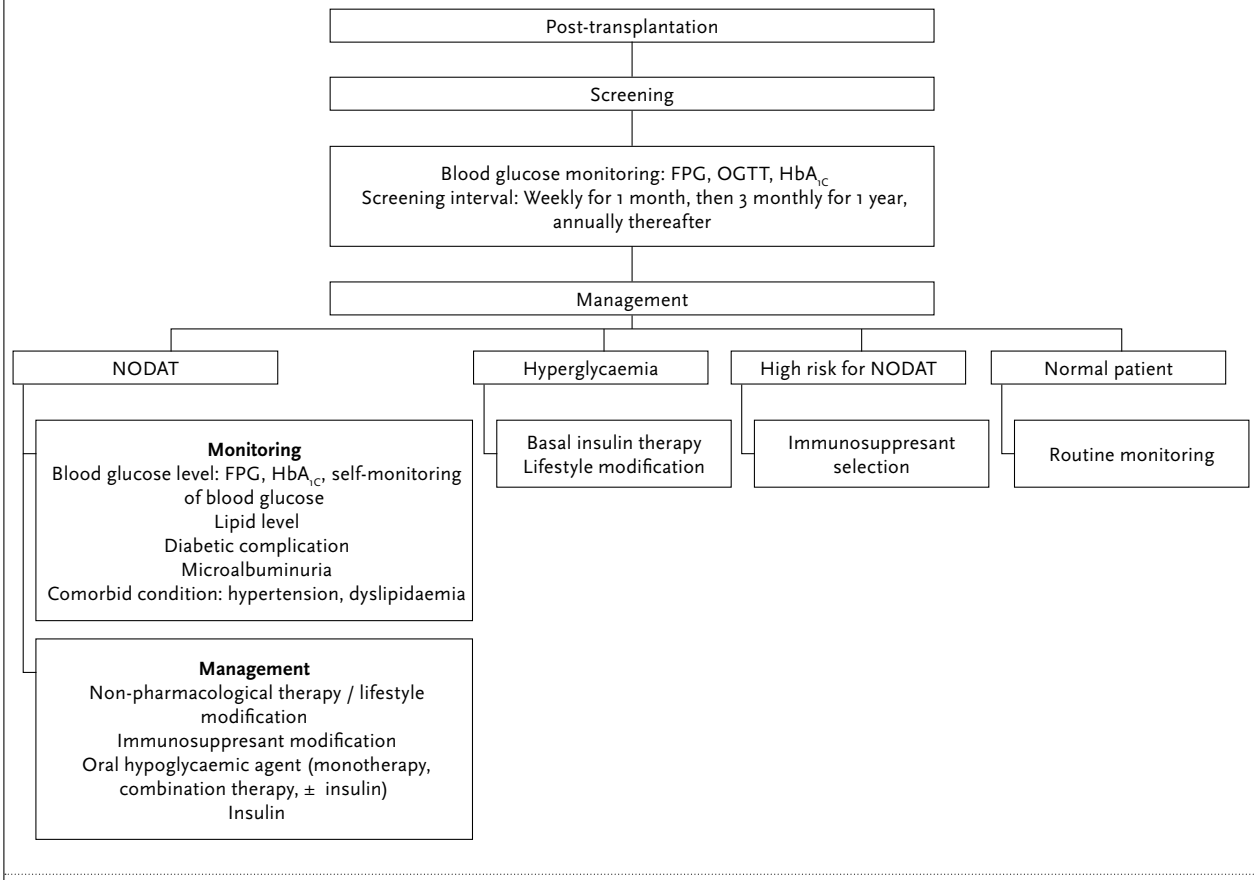
According to the 2009 KDIGO guideline,[11] it is recommended to screen all non-diabetic kidney transplanted patients for NODAT with FPG, OGTT and/or HbA_{1C} testing at least weekly for the first four weeks, followed by every three monthly for one year and annually thereafter. These screening tests are also suggested to be performed on patients after initiation or substantial increases in the dose of CNIs, mTORi or corticosteroids.[11] The diagnosis of NODAT is based on the criterion set by the WHO and ADA.[6] Blood glucose monitoring is essential as studies have demonstrated that occurrence of hyperglycaemia during the initial period of post-renal transplantation[49,50] and IFG or IGT[6,51] are strong predictors for the development of NODAT. However, there are other opinions with regards to NODAT screening. A Norwegian study recommended a combination of OGTT at three months post-transplantation when the FPG is between 95 and 124 mg/dl (5.3-6.9 mmol/l) and/or when HbA_{1C} is ≥5.8%.[52] Rodringo *et al.*[53] recommended the use of the score of Chakkera *et al.*[54] at pre-transplantation to predict NODAT while the San Antonio Diabetes Prediction Model or Framingham Offspring Study-Diabetes Mellitus algorithm are recommended from the first year onwards post-transplantation. A summary of the screening and management strategies recommended by various guidelines[6,11,40] and studies[12,15,21-24,42-44,47,48,52,55-59] is given in *figure 2*.

Figure 1. *Pre-transplantation screening and prevention of NODAT*



OGGT = oral glucose tolerance test; FPG = fasting plasma glucose.

Figure 2. *Post-transplantation screening and management*



OGGT = oral glucose tolerance test; FPG = fasting plasma glucose.

NODAT

When NODAT develops, patients should be routinely monitored for FPG and HbA_{1C}. HbA_{1C} should be monitored three monthly[6] with a target of 7-7.5%.[11] Targeting HbA_{1C} ≤6.0% should be avoided especially if hypoglycaemic reactions are common.[11] Careful interpretation of the HbA_{1C} test result is needed in patients with anaemia or kidney impairment.[6] Self-monitoring of blood glucose is encouraged, particularly for patients on non-pharmacological therapy and receiving oral hypoglycaemic agents or insulin.[6] The suggested target of fasting blood glucose in the morning is 90-130 mg/dl (5.0-7.2 mmol/l) and the target before bedtime is 110-150 mg/dl (6.1-8.3 mmol/l).[40]

Annual screening of the lipid profile is advocated in NODAT patients, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides[6] due to frequent changes in glycaemic control in these patients and the effect of this on the lipoprotein level. Besides, NODAT patients need to be screened for diabetic complications annually, such as retinopathy and neuropathy.[6] Consideration may also be given to screening for the presence of microalbuminuria, although the validity of such screening has not been verified.[6] Lifestyle modification including dietary, exercise, weight control and smoking cessation is emphasised as initial non-pharmacological therapy to improve glycaemic control in NODAT and early post-transplant hyperglycaemic patients.[22,48,60]

Immunosuppressive regimen

When NODAT develops, modification of the immunosuppressive regimen may be considered to reverse or improve diabetes after weighing the risk of rejection and other potential adverse effects.[11] The changes suggested by KDIGO[11] include:

1. Reducing the dose of Tac, CsA or corticosteroids;
2. Discontinuing Tac, CsA or corticosteroids;
3. Replacing Tac with CsA, MMF or AZA;
4. Replacing CsA with either MMF or AZA.

However, a combination of CNI and mTORi therapy[21,22,30,31] and switching from Tac to Sir is not recommended because

it can worsen insulin resistance.[61] Tapering the dose of Tac[48] and Sir[30] to a lower range is not recommended due to the rejection risk, particularly in high immunological risk.

Steroid-sparing strategies have been shown to reduce NODAT incidence requiring any treatment. Although these strategies were associated with an increase in acute rejection, there was no increment in the mortality due to graft loss.[59,62] These strategies may be safe, provided antibody induction treatment is prescribed a few days post-kidney transplantation or after 3-6 months if such induction is not applied.[59] Prednisolone withdrawal is generally not recommended due to the risk of acute rejection, despite marginal effects on glucose control. Thus, a low maintenance dose of prednisolone 5 mg/day is advocated.[51,63] Careful selection of patients with low immunological risk is advisable if prednisolone withdrawal is to be considered.[63,64] In a 12-month study a regimen based on belatacept, a selective T-cell costimulation blocker, was associated with better cardiovascular and metabolic risk profiles, with lower blood pressure and serum lipids, and less incidence of NODAT as compared with CsA.[65] Currently, an on-going randomised study is being conducted to assess whether belatacept is an appropriate alternative immunosuppressive agent against Tac for NODAT patients.[66]

Ghisdal *et al.*[15] suggested an algorithm for the management of immunosuppressant regimens aiming to reduce the risk of NODAT and improve established NODAT. The first choice of immunosuppressant depends on the patient's immunological risk. High immunological risk is defined as those patients with a third or fourth transplantation, second transplantation if the first was lost in less than two years, presence of anti-HLA antibodies or high panel-reactive antibodies and five to six HLA mismatches. These patients are recommended to undertake regimens consisting of Tac, corticosteroid and mycophenolic acid (MPA). Whereas regimens of either CsA or belatacept plus corticosteroids and MPA are suggested for those with low immunological risk but high NODAT risk. When NODAT develops, the level of Tac and MPA should be monitored to ensure better glucose control. With Tac regimens a trough level of 6-8 ng/ml should be achieved in low immunological-risk patients and 8-10 ng/ml in high immunological-risk patients, while the area under the curve (AUC) of MPA should be 30-60 mg h/l.[67] For patients with CsA regimens, the strategy of tapering off the steroid while maintaining MPA at the optimal AUC level can be considered. When diabetes is no longer controllable (HbA_{1C} >7% and/or insulin requirement), switching from Tac to CsA in high immunological-risk patients is advised, whereas a switch from CsA to belatacept may be considered when the immunological risk is low. Tac offered a better protection against rejection than CsA despite higher incidence of NODAT.[7] However, long-term data are not available to justify the benefit of diabetes control in Tac conversion therapy.[22,48]

Oral glucose-lowering agents

When initial glycaemic control with immunosuppressant modification and non-pharmacological therapy fails, oral glucose-lowering agents may be prescribed as the first-line agents, as a traditional standard approach.[6] The choice of drugs should be based on pharmacological properties[24] with benefits weighed against side effects including weight gain and hypoglycaemia,[68] and potential drug-drug interactions with immunosuppressant regimens, which may lead to glomerular filtration impairment, weight gain and/or risk of osteoporosis.[23,47] Besides, with advancement of atherosclerosis, these agents serve to improve rather than worsen the risk of progressive cardiovascular disease. Thus, the recommended first-line oral glucose-lowering agents are mainly insulin secretagogues, including sulfonylurea (glipizide) and meglitinides (repaglinide and nateglinide).[48,58] Meglitinides are recognised to be the safest due to no interaction with the CNI, no renal or liver insufficiency effect and are the first choice drug for elderly transplant patients at low dose.[6] Metformin, an insulin sensitiser, is recommended for use only if the patient's glomerular filtration rate is more than 60 ml/min/1.73m^2.[48,69] Thiazolidinedione usage has yielded variable results. In a study, it was shown to be safe to use up to 37 months post-transplant.[69] However, thiazolidinediones should be used with caution due to various side effects including oedema, weight gain and fracture.[22,23,43] Metformin and pioglitazone are claimed to be useful in treating preexisting diabetes mellitus and NODAT in patients with good allograft function,[69] but not as prevention strategies.[44] Sarno *et al.*[24] suggested that the use of oral glucose-lowering agents should be based on the patient's diabetic risk factors and the probable diabetogenic effects aroused. When combination therapy is required, metformin may be used with glipizide, sitagliptin or insulin, while sitagliptin may be used with insulin.[48] Nonetheless, dose adjustment is needed for sitagliptin in renal insufficient patients. Currently, there is no established safety and efficacy evidence to support the use of incretin-based therapy in the treatment of NODAT.[22,43,48]

Insulin therapy

When glycaemic control fails to achieve FPG <120 mg/dl (6.7 mmol/l), PG <160 mg/dl (8.88 mmol/l) or HbA_{1C} <7%, insulin in combination with oral glucose-lowering agents is often initiated.[70] In order to control late afternoon or early evening glucose level, intermediate-acting neutral protamine Hagedorn (NPH) insulin would be useful. If the approach fails to control the postprandial glucose level,

short-acting insulin aspart or lispro may be added into the routine treatment. NPH insulin, glargine or detemir insulin may be given in addition at night to control the surge of morning blood glucose.[70]

Chakkera *et al.*[49] showed that hyperglycaemia post-transplantation is significantly associated with the development of NODAT. Thus, intervention for hyperglycaemia is needed in order to prevent NODAT. Experts have suggested that keeping the average PG at <180.2 mg/dl (10 mmol/l) and HbA_{1C} <8%, is safe in the first post-transplantation week.[48] Hecking *et al.*[55] proposed that for post-transplanted patients with evening hyperglycaemia (glucose level >200 mg/dl or 11.10 mmol/l), early basal insulin is effective in reducing both NODAT development and HbA_{1C}. In the randomised study conducted by Hecking *et al.*[55] the basal insulin group was first treated with a morning dose of 6, 8, or 10 IU of NPH insulin when the previous evening blood glucose was >140 mg/dl (7.8 mmol/l), 180 mg/dl (10.0 mmol/l) or 240 mg/dl (13.3 mmol/l). Short-acting insulin will be used to further correct the hyperglycaemia event during postoperative inpatient care, followed by NPH insulin dose increment. The normoglycaemic goal was 110-120 mg/dl (6.1-6.7 mmol/l). The control group received conventional anti-diabetic and anti-hyperglycaemic treatment with short-acting insulin and/or oral glucose-lowering agents when the blood glucose level was ≥180 mg/dl (10.0 mmol/l). As a result, the treatment group had a 37% lower chance of NODAT (odds ratio 0.27; 95% confidence interval, 0.10-0.72) than the control group while HbA_{1C} was on average 0.38% lower in the treatment group than the control group.[55]

In a guideline developed by the International Diabetes Federation,[40] insulin is recommended to manage acute hyperglycaemia when the PG level is ≥250 mg/dl (13.9 mmol/l). A continuous infusion of insulin 50 IU/hour is recommended to maintain a morning blood glucose level between 80-110 mg/dl (4.4-6.1 mmol/l). When the condition is stabilised, conventional glycaemic maintenance level will be implemented and conventional type 2 diabetes mellitus therapeutic practice may be adopted. However, when chronic hyperglycaemia occurs, blood glucose targets should be individualised and a conventional diabetes therapy is adjusted accordingly to control the patient's blood glucose level. Thus the precise intervention requirement will be individualised to achieve optimum outcome.[40]

Comorbid conditions

Comorbid conditions, mainly dyslipidaemia and hypertension, should be aggressively treated to reduce the risk of cardiovascular morbidity and mortality.[6,23] The target of LDL-C in the post-kidney transplant patient is ≤100 mg/dl (2.60 mmol/l) or ≤70 mg/dl (1.8 mmol/l) for those with established cardiovascular disease.[11,42] Medical nutritional therapy should be initiated while statins may be considered for patients with LDL-C of 100-129 mg/dl (2.60-3.35 mmol/l). Whereas, patients with LDL-C ≥130 mg/dl (3.38 mmol/l) should receive statins as primary treatment plus a medical nutritional therapy.[6] Pravastatin and fluvastatin[48,56] are the preferred statins, since they are not metabolised by CYP 3A4.[43] Furthermore, exposure to Sir and glucocorticoids is associated with hypertriglyceridaemia. Thus, close monitoring of the degree of hypertriglyceridaemia is warranted and treatment with fibrates may be required. However, if the patient is prescribed a statin, fish oil is an alternative instead of fibrates, which are associated with the risk of rhabdomyolysis.[43]

A 50-90% incidence of hypertension is observed among kidney transplant patients and it is an independent risk factor for cardiovascular disease.[11] The recommended target for blood pressure control by ADA[6] and KDIGO[11] is <130/80 mm/Hg for a type 2 diabetes mellitus patient. However, Jenssen *et al.*[48] suggested that the high blood pressure should be treated with caution in NODAT patients with a proposed target not lower than 140/90 mmHg. This is to prevent the development of orthostatic hypotension due to aggressive treatment, especially in patients with extensive arteriosclerosis and autonomous neuropathy. Generally, there is no specific contraindicated antihypertensive drug in post-kidney transplant patients and any class of it may be used.[11] The initial choice is weighted by the benefits against the presence of post-transplant complications while monitoring closely for any adverse effects and drug-drug interactions.[11] Immunosuppressive agents including corticosteroids and CsA may also lead to blood pressure elevation[11,43] and justification is needed in considering dose adjustment, immunosuppressive agents selection and modification. Aspirin therapy should be given for patients with cardiovascular disease.[48]

CONCLUSION

Currently, the diagnostic criteria for IFG, IGT and NODAT set by the WHO and ADA are widely used. The use of these criteria allows early detection and prompt action to be taken to manage the condition. Apart from using OGTT and FPG, as recommended by WHO and ADA, the KDIGO has suggested HbA_{1C} as an additional screening parameter for NODAT after the kidney transplantation. NODAT and type 2 diabetes mellitus have many similarities in terms of risk factors, screening, monitoring, management and prevention strategies. Early detection and proper intervention should be taken during pre- and post-kidney

transplantation to reduce the incidence of NODAT and the consequent cardiovascular risk factors. Individualisation of immunosuppressive therapy also plays a role in reducing the risk and ameliorates the NODAT. Selection of immunosuppressive and anti-diabetic regimens should be justified based on the benefits, immunological risk, risk of NODAT and the probability of drug-drug interaction.

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ORIGINAL ARTICLE

Recommendations for diagnosis and treatment of spondylodiscitis

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ABSTRACT

Background: Spondylodiscitis, also known as vertebral osteomyelitis, is a destructive disease with high morbidity and mortality. Diagnosis is often delayed because of the rarity of the disease and the fact that early symptoms are often non-specific. There are currently no national guidelines on the diagnosis and treatment of spondylodiscitis in the Netherlands.

Methods: We performed a single-centre retrospective cohort study examining 49 patients over 18 years of age treated for spondylodiscitis in a six-year time period.

Results: Mean age of patients was 69 years (range 40-89). Most patients underwent an MRI scan to confirm diagnosis (n=30). In 39 patients a microorganism was found, most commonly *Staphylococcus aureus* (n=14), *Streptococcus* species (n=11) and Gram-negative bacteria (n=11). All patients were treated with antibiotics. Thirty-seven patients received antibiotic treatment for at least six weeks, while 17 patients were treated for 90 days or longer. In 13 patients no adequate treatment was started until culture results were available. Eleven patients underwent surgery after their diagnosis. Two patients had a recurrence.

Conclusion: We recommend that, when considering spondylodiscitis as a possible diagnosis, all patients should undergo thorough physical examination, neurological screening, blood tests for infection and blood cultures. An MRI scan should be performed, followed by a PET-CT scan when results are inconclusive. Ideally a CT-guided biopsy is performed before treatment is started. Awaiting culture results all patients should receive broad-spectrum antibiotics. Targeting only Gram-positive microorganisms in empiric treatment will lead to a delay in adequate treatment in a substantial group of patients. A multidisciplinary approach is advocated.

KEYWORDS

Diagnosis, guideline, spondylodiscitis, treatment

INTRODUCTION

Spondylodiscitis is a rare but serious infection of the intervertebral disc with possibly devastating outcome. The peak incidence is in patients under 20 years of age and between 50 and 70 years of age. The incidence ranges from 0.4- 2.5 per 100,000 per year.[1-3] Patients present with a variety of symptoms including back pain, fever, nausea, and weight loss. There is often a delay in diagnosis due to the nonspecific nature of symptoms.[4,5]

Spondylodiscitis occurs secondary to a variety of causes, most notably bloodstream infections (e.g. *Staphylococcus aureus*) and after surgery.[6] The most commonly found pathogen responsible for spondylodiscitis is *S. aureus*, but coagulase-negative staphylococci, *Streptococcus* species, *Pseudomonas aeruginosa, Escheria coli*, and fungi such as *Candida albicans* are also regularly found.[2,5,6]

Diagnosis of spondylodiscitis is difficult. The diagnostic tools most often used are blood cultures, MRI scans, and vertebral biopsies.[1] MRI scan has proven to be the modality of choice for most physicians with high sensitivity even early in the disease process.[7]

Treatment regimens differ between hospitals. The main variation seems to be in choice, route of administering, and duration of antibiotic therapy.[5,8,9] Evidence suggests that patients should be treated for at least six weeks with antibiotics and preferably 12 weeks.[3,10] Due to the lack of randomised controlled trials there is still no high-level evidence on which treatment regimen provides the best outcome in patients with spondylodiscitis. Currently there is no nationwide protocol for spondylodiscitis in the Netherlands.

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The aim of this study was to evaluate the treatment of spondylodiscitis in our hospital. We evaluated the diagnostic process, the treatment, and patient outcome to determine whether there are indications for a preferred treatment strategy.

MATERIALS & METHODS

A single-centre retrospective cohort study was performed in a high volume non-academic hospital. Data were collected of patients over 18 years admitted to the internal, neurology or orthopaedic department from 1 January 2007 until 31 March 2013. All patients were registered in the hospital registration system as having been diagnosed with spondylodiscitis. Patients were excluded if the diagnosis of spondylodiscitis was not confirmed either by characteristic imaging, surgical verification, a positive culture, or a good response to treatment.

Diagnosis of spondylodiscitis was defined by clinical findings and characteristic changes on magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography CT (PET-CT), a positive culture (blood, cerebrospinal fluid, disc, or another source), or a good response in patients with suspected spondylodiscitis to treatment either with or without a positive finding on imaging or culture.

Data were collected on start, finish and adjustments of antimicrobial treatment. Several patients also needed surgical intervention. Of these patients the type of surgery was registered and whether or not tissue was collected.

RESULTS

Study population

Data were collected from 78 patients who were encoded in the system as having spondylodiscitis. After examining files a total of 49 patients met the inclusion criteria. Of these patients 29 were male and 20 female. Mean age of the study population was 69 years, ranging from 40 to 89 years.

Most patients (n=20) had an infection in the lumbar intervertebral discs, nine patients in the thoracic disc, and five patients in the cervical disc. Fifteen patients had an infection in more than one segment.

Of the 49 patients, 17 had back problems in their medical history. Nine patients had spinal surgery previous to their episode of spondylodiscitis. In other patients no other focus of origin of the infection could be found.

Diagnosis

Radiology

MRI scan was most commonly used, in 30 patients. In four patients only a conventional X-ray was used *(table 1)*. Two patients were only diagnosed by repeating the MRI scan. One patient had a positive lesion on a FDG-PET/CT scan, which was first diagnosed as a malignancy but after biopsy appeared to be infectious.

Table 1. *Radiology*

Technique	No of patients
MRI	29
MRI + X-ray + CT scan	1
PET scan	12
X-ray	4
CT scan	3
Total	49

Bacteriology

Cultures were obtained from 44 patients: 31 blood cultures were taken, nine patients had material taken for biopsy, five patients underwent both a biopsy and had blood cultures taken, and for one patient a sputum sample was examined.

In 39 patients microorganisms were identified in the material obtained for bacteriological examination *(table 2)*. Most of these (n=14) were *S. aureus*. Eleven patients had Gram-negative bacteria, and another 11 had a species of *Streptococcus*. In three patients a coagulase-negative staphylococci was seen. There were two patients with tuberculosis and one with a fungal infection (*C. albicans*).

Antibiotic treatment

Two patients who were diagnosed with tuberculosis were treated with tuberculostatics. Of the other 47 patients, there were data on the start and finish of antibiotic treatment of 44 patients. The treatment consisted of intravenous antibiotics and after a certain period an oral regimen. Eleven patients received only intravenous treatment and three patients were treated with oral antibiotics only. Thirty-seven patients were treated for a total of at least six weeks, 17 patients were treated for at least 90 days. The mean number of days that patients received antibiotic treatment are shown in *table 3*.

Table 2. *Micro-organisms*

Pathogen	# of patients
S. aureus	14
Gram-negative bacteria	11
Streptococci	11
Coagulase-negative staphylococci	3
Mycobacterium tuberculosis	2
Candida albicans	1
Total	42 (3 patients with 2 bacterial types)

Table 3. *Antibiotic treatment*

Duration	Median (days)	Minimum	Maximum
Intravenous antibiotic treatment	37	4	141
Oral antibiotic treatment	47	0	206
Total antibiotic treatment	89	4	222

From 42 patients there were data available on the number of days between start of antibiotic treatment and the start of the appropriate treatment for the specific micro-organism found in culture. Antibiotic treatment was adjusted as soon as the results of the Gram stain and culture were known. The initial treatment proved adequate in 29 patients. The remaining 13 patients had a median delay of adequate treatment of 3 days, ranging from 1-10 days.

Surgery

Eleven patients underwent surgery after their diagnosis of spondylodiscitis. In seven patients the indication for surgery was a poor response to initial treatment. In one patient a biopsy was performed because additional material for bacteriological examination was required, and three patients were operated on because of decreasing neurological functions. No patients received only surgical treatment.

Recurrence

Two patients had a recurrence of spondylodiscitis during the study period, both within six months after the initial diagnosis. One patient was adequately treated for three months with antibiotics before his recurrence one month after finishing his treatment. The second patient had a recurrence during treatment with oral antibiotics after a period of six weeks of intravenous antibiotics, but this recurrence was treated in another hospital.

DISCUSSION

A retrospective study was performed of 49 patients treated for spondylodiscitis in a high volume non-academic hospital over a period of over six years. Data were collected on diagnosis, culture, surgery and antibiotic treatment.

The mean age of patients was 69 years. Only patients over 18 years of age were included because children with spondylodiscitis are referred to an academic hospital in our region. In other studies a peak incidence in (early) childhood is often found.[1,6]

One of the usual predictors of spondylodiscitis is recent back surgery.[5,8] However, just 17 patients had a history of back problems. Only nine of those had undergone back surgery prior to their diagnosis of spondylodiscitis. This indicates that even without recent back surgery, spondylodiscitis should be considered as a possible diagnosis in patients with unexplained fever.[1,4]

Initial diagnosis of spondylodiscitis is difficult due to the combined delaying factors of aspecific symptoms and the relative rarity of the disease. Almost all patients in the current study were diagnosed correctly using radiological methods. Our results suggest that as soon as there is a suspicion of spondylodiscitis, radiology can provide an indication whether the suspected diagnosis of spondylodiscitis is correct. Most patients underwent either an MRI scan or a PET-CT scan. Because of increasing availability and high sensitivity and specificity the first diagnostic method of choice is the MRI scan.[11]

To provide adequate treatment of the microorganism it is essential that material for Gram stain and culture is collected prior to the start of antibiotic treatment. Blood cultures are an easy and effective way to determine pathogens.[1,8] CT-guided biopsy of the intervertebral disc has been proven to be a helpful diagnostic method to determine the microorganism responsible for spondylodiscitis in patients in whom no microorganism is found in the blood cultures or who do not respond well to initial antibiotic treatment.[12-14]

In most cases there were cultures obtained to determine the pathogen responsible for the spondylodiscitis. There were seven patients in whom no material was obtained for culture. In several cases this was because antibiotic treatment had already been started, but in some patients there was no clear reason why culture was omitted from the diagnostic process.

One-third of patients were diagnosed as being infected by *S. aureus*. This is a lower percentage than found in the literature where over half of all patients had an infection with *S. aureus*,[1,5,10] with percentages ranging from 15 to 84%.[1,6] There were only two patients with spondylodiscitis caused by tuberculosis, which is also less than expected in developed countries when looking at the literature.[1]

The antibiotics started were usually adequate for the most frequently found micro-organisms. There were 13 patients where no adequate treatment was started and where a switch to a different type of antibiotic, based on the results of the cultures, was necessary. Almost all patients were infected with *S. aureus,* Gram-negative bacteria or *Streptococcus* species. Especially these micro-organisms should be taken into consideration when starting antibiotic treatment before results from cultures are known.

During the period examined there was no nationwide protocol for the treatment of spondylodiscitis. All patients were treated with antibiotics. The median number of days that patients were treated with antibiotics was 87, which is largely consistent with the consensus that patients with spondylodiscitis should be treated for at least 6-12 weeks with adequate antibiotic therapy.[3,10]

Surgical treatment of spondylodiscitis can be necessary when radiological imaging shows destruction of the vertebrae, a spinal abscess, deterioration of neurological functions, or when patients continue to deteriorate despite adequate antibiotic treatment.[3,15] Eleven patients in our study underwent surgery. More than half of these patients did not have a good response to initial treatment with only antibiotics. A relapse of spondylodiscitis was found in two patients, which is consistent with other studies.[3] Both these patients were treated with antibiotics and had not undergone surgery.

There were some limitations in our study. Firstly, this is a retrospective study that is descriptive in terms of treatment given. Also, there were no data collected on outcome in infection and function.

Based on the data collected and current literature we can make some recommendations. Spondylodiscitis should be considered as a possible diagnosis in all patients presenting with symptoms of a systemic infection. A thorough physical examination including a neurological screening should be performed followed by blood tests for infection and blood cultures. An MRI scan should be performed to determine the level and extent of the infection and to rule out other possible diagnoses. When there is doubt about the diagnosis a PET-CT scan can provide additional information. Whenever possible, a CT-guided biopsy should be performed to help determine the micro-organism responsible for the infection before starting antibiotic treatment. Patients should start with a broad-spectrum intravenous antibiotic awaiting further results from the cultures, since initial treatment for only *S. aureus* seems insufficient. A multidisciplinary approach by orthopaedic surgeons, infectiologists, microbiologists and neurologists is warranted. We are awaiting guidelines for diagnosis and treatment of spondylodiscitis.

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ORIGINAL ARTICLE

Predictors of colorectal neoplasia after polypectomy: based on initial and consecutive findings

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ABSTRACT

Background: Colorectal adenoma patients are kept under surveillance because of the risk of developing metachronous neoplasia. The aim is to determine predictors of neoplasia development after polypectomy.

Methods: It is an observational cohort study. 433 Patients who had ≥1 adenoma removed between 1988 and 2004 were included, with follow-up until 2010. Multivariate analysis of patient and adenoma characteristics was performed at initial colonoscopy and at consecutive positive examinations. The main outcome measured was the development of metachronous (advanced) adenomas during follow-up.

Results: Median follow-up was 85 months. Multivariate analysis identified male sex, ≥3 adenomas, high-grade dysplasia and age ≥55 years as risk factors for metachronous lesions at first surveillance. Analysis using life expectancy as a timescale showed ≥3 adenomas to be the only predictive factor. The time to second or third metachronous adenoma did not depend on the number of adenomas. Patients with ≥3 adenomas were five years older at the time of their first polypectomy compared with those with fewer adenomas, but of the same age at the first recurrence. Prevalence of high-grade dysplasia was associated with age and high-grade dysplasia in the prior adenoma independent of time interval.

Conclusions: Adenoma development after polypectomy occurs in a regular and repetitive way. Our data suggest that only the interval between the initial colonoscopy and the first follow-up colonoscopy should be based on initial findings, i.e. number of adenomas, and that subsequent colonoscopies can be planned at predetermined intervals.

KEYWORDS

Adenoma, colonoscopy, colorectal neoplasms, polypectomy, surveillance

INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer mortality in Western countries.[1,2] Most colorectal cancers develop from a benign precursor lesion, the adenoma. Adenomas with so-called advanced features have the highest risk to develop into CRC. The definition of an advanced adenoma is >25% villous histology, and/or size larger than 1 cm, and/or presence of high-grade dysplasia.[3-6] Removal of adenomas has been shown to reduce the incidence and mortality of CRC.[3,7-10] Following polypectomy of adenomas, patients are generally kept under endoscopic surveillance because of an increased risk of developing metachronous neoplasia.[3,6]

Apart from the risk of complications, surveillance endoscopies are a significant burden in terms of medical resources and costs.[11-14] It is therefore important to identify predictive factors for adenoma recurrence in order to select patients for follow-up and to determine appropriate surveillance intervals. In the current guidelines, risk stratification is based on studies that focused on adenoma and patient characteristics at first colonoscopy.[4,8,15]

Since 1988, follow-up after polypectomy at our Institution has been done following the national guidelines.[16,17] This allowed us to analyse data from a long follow-up period with consecutive endoscopies. Therefore, in this study we not only focused on the results of the first polypectomy, but used the findings of all examinations during this follow-up

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period. The objective of this study was to determine predictive factors for the development of adenomas and advanced neoplasia after polypectomy. Based on the results, a proposal for appropriate surveillance intervals is formulated.

MATERIALS AND METHODS

Patient selection

A database search was performed in the Dutch Pathological Anatomic National Automatic Archive (PALGA) in order to retrieve records of patients who had undergone polypectomy of at least one colorectal adenoma at our institution between 1988 and 2004. Up to July 2010, data were retrospectively collected from the medical charts. Subjects were included if they were 18 years or older and had undergone polypectomy of at least one histologically proven adenoma during a complete colonoscopy. Patients were excluded if any of the following risk factors for CRC were present: a personal medical history of CRC, Lynch syndrome or other hereditary predisposition syndrome or inflammatory bowel disease. Also patients with a liver transplantation were excluded because of their increased risk of advanced lesions.[18]

During the study period the national guidelines underwent some modifications with respect to follow-up after polypectomy of adenomatous polyps. From 1988-1997, the national guidelines advised a yearly follow-up colonoscopy after polypectomy until a 'clean' colon. And then again after three years in case of multiple or after five years in case of a single adenoma.[17] In 1997 the colonoscopy after one year was no longer deemed necessary.[4,19] In 2001, the guidelines were revised, recommending follow-up after six years in case of ≤2 adenomas, and after three years in case of ≤3 adenomas.[16]

A time interval of at least six months between examinations was used to define metachronicity of adenomas, which is consistent with similar studies.[15,20,21] For patients to be included in this study, data from at least one complete surveillance colonoscopy had to be available. As a rule all lesions had to be removed and histologically categorised. If patients had more than one lesion, they were categorised according to their most advanced lesion. Basically all polyps were sent for histology and we estimate that less than 10% were not. If no histology was obtained, polyps were not included in the analysis. Adenoma location was defined as proximal or distal, relative to the splenic flexure. Adenoma size was derived from the histopathological report. When the original histology reports were incomplete or described moderate-grade dysplasia, samples were revised by the pathologist (HH) and dysplasia was categorised as low-grade or high-grade according to current guidelines.[22]

Statistical analysis

Associations between patient and adenoma characteristics were analysed using the Chi-square test. Associations between these characteristics and life expectancy and age were tested by the Mann-Whitney U-test. Univariate and multivariate Cox regression analyses with patient and adenoma characteristics were performed using the interval between colonoscopies as a timescale to identify possible risk factors for the development of metachronous adenomas and carcinomas during follow-up. Risk factors that had a p-value <0.15 at univariate analysis were incorporated in a multivariate analysis using a stepwise backward procedure ending with p<0.05. End of follow-up was determined by the last complete colonoscopy or death. Risks were expressed using hazard ratios (HR) with their 95% confidence intervals (CI). A CI not including the value 1.0 and a p-value <0.05 indicated a significant association. Data were analysed with SPSS software version 17.0.

Due to the association between rate of adenoma recurrence with sex and age, and because of differences in sex and age among the various subgroups of patients, the analyses were repeated by log-rank test using an age-related timescale.[23,24] Risks were expressed using odds ratios (OR) with their 95% CI. In order to adjust for sex, age and birth cohort, the median life expectancy – projected on a negative x-axis – was chosen as a timescale. Median life expectancy at the first examination was derived from the sex-specific annual reports of mortality in the general Dutch population provided by the Central Bureau of Statistics (CBS).[25] These mortality data were also used to calculate the standardised mortality rate (SMR) of the patients as the ratio between observed and expected deaths. Differences in ranges of age at death were studied by means of the F-test. Left censoring of data was involved in the analysis of life expectancy. However, since the application to perform this calculation is not provided by commonly available software, the calculations were performed using Excel software (version 2007).

RESULTS

Patient and baseline adenoma characteristics

In total, 488 patients were identified. Of these, 55 were excluded because one or more previously identified risk factors for CRC were present, or because of incomplete data. The final analysis therefore included 433 patients (mean age 55, range 24-82, 41% males). Twenty-nine patients had an adenoma in their history and their follow-up for this study started when their first metachronous lesion was removed. A total of 404 patients had their first adenoma diagnosis during the study period. In total, 239 adenomas were revised by our pathologist to meet current guidelines. Our patient group had an

estimated SMR of 1.10 (95% CI 0.74-1.42, p=0.637). All causes of death during follow-up were known and were not related to colorectal cancer.

Adenoma characteristics at baseline are summarised in *table 1*. Baseline colonoscopy revealed ≥3 adenomas in 67 cases (16%). An advanced adenoma was found in 251 cases (58%).

Associations between patient and adenoma characteristics at baseline

Male sex in the 404 newly diagnosed patients was associated with having ≥3 adenomas (p=0.04). Having ≥3 adenomas was also associated with high-grade dysplasia (p=0.003), size ≥1 cm (p=0.001) and proximal location (p<0.001). High-grade dysplasia was associated with size ≥1 cm (p<0.001) and villous features (p<0.001). The median life expectancy at the time of diagnosis was lower in cases with ≥3 adenomas than in those cases with fewer adenomas (24.9 vs 30.0 years respectively, p <0.001).

Follow-up

The median follow-up period was 85 months (range 9-260). The median number of colonoscopies that had been performed during follow-up was 2 (mean 2.3, range 1-7). During follow-up, 219 out of the 433 patients (51%) developed at least one adenoma. Characteristics of these metachronous findings are depicted in *table 1*. Compared with baseline adenomas, incident adenomas were more often smaller than 1 cm, generally showed tubular growth, and more often low-grade dysplasia.

The occurrence of these metachronous findings during follow-up in the 404 newly diagnosed patients from diagnosis until observed mortality is shown in *figure 1*. During patients' lifetime, new adenomas occurred after an interval of about 6-8 years.

During follow-up, 86 patients (20%) were diagnosed with an advanced adenoma and two patients (0.7%) with CRC. In the first patient who developed CRC (male, 59 years at the time of diagnosis of first adenoma), one small tubular adenoma was found at initial colonoscopy. A colonoscopy after two years because of symptoms proved normal, whereas five years later CRC was detected at the third colonoscopy. The second patient (female, 51 years at diagnosis of first adenoma) initially had one advanced adenoma (larger than 1 cm, high-grade dysplasia with tubulovillous features, distally located). After five years she had a second colonoscopy which proved to be negative. Her third colonoscopy took place after ten years and demonstrated one small villous adenoma with low-grade dysplasia. CRC was diagnosed at the fourth colonoscopy, 15 years after the initial colonoscopy. Neither of these two tumours were tested for microsatellite instability of tumour DNA or the immunohistochemical expression of mismatch repair genes.

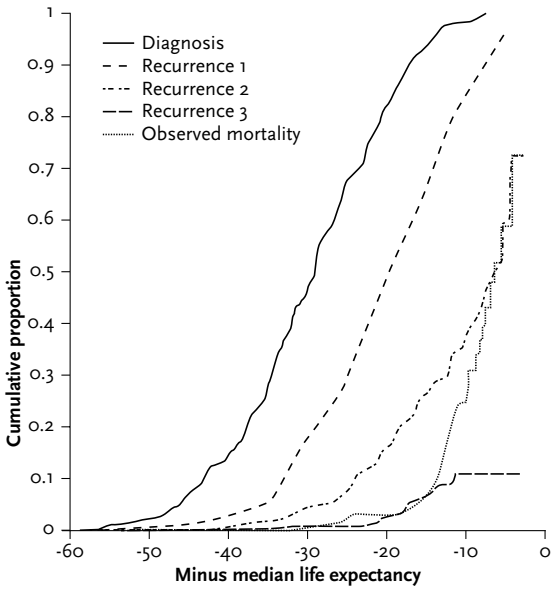
Risk factors for metachronous adenoma at first surveillance

Univariate analysis revealed male sex (p=0.001), age ≥55 years (p=0.004), ≥3 adenomas at colonoscopy (p=0.001), proximal location (p=0.01) and high-grade dysplasia (p=0.03) to be risk factors for first metachronous adenoma.

Table 1. *Adenoma characteristics: findings at baseline and follow-up colonoscopies*

	Initial colonoscopy (n = 433)	Adenoma recurrence (n = 219)
Number of adenomas		
One	284 (65.6%)	147 (67.1%)
Multiple	149 (34.4%)	72 (32.9%)
<3 adenomas	366 (84%)	186 (85%)
>3 adenomas	67 (16%)	33 (15%)
Histology		
Tubular	234 (54%)	157 (71.6%)
Tubulovillous	149 (34.4%)	49 (22.4%)
Villous	37 (8.5%)	5 (2.3%)
Serrated	7 (1.6%)	4 (1.8%)
Unknown	6 (1.4%)	2 (0.9%)
Size		
<1 cm	257 (59.4%)	193 (88.1%)
>1 cm	160 (37%)	21 (9.6%)
Unknown	16 (3.6%)	5 (2.3%)
Degree of dysplasia		
Low-grade	273 (63%)	185 (84.5%)
High-grade	156 (36%)	31(14.2%)
Unknown	4 (0.9%)	1 (0.5%)
Carcinoma		2 (0.7%)
Location		
Proximal	136 (31.4%)	113 (51.6%)
Distal	284 (65.6%)	96 (42.9%)
Unknown	13 (3%)	10 (4.6%)

Figure 1. *Diagnosis, metachronous adenomas and death during follow-up*



The occurrence of metachronous adenomas during follow-up from diagnosis till observed death on a life expectancy scale. Adenomas recurred with a median interval of about eight years.

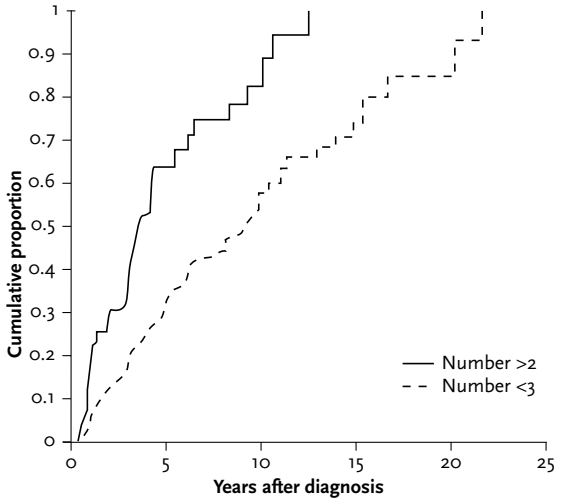
Multivariate analysis showed male sex (HR=1.59; 95% CI 1.18-2.13; p=0.003), ≥3 adenomas (HR=1.92; 95% CI 1.34-2.77; p<0.001) and age (HR=1.04, 95% CI 1.02-1.05, p<0.001) to be independent risk factors. A Kaplan-Meier plot stratified for number of lesions, unadjusted for age or sex, is shown in *figure 2*. A 30% cumulative proportion was found after 2.5 years in patients with ≥3 adenomas, and after five years in patients with 1-2 adenomas.

As sex and age were strongly associated with the number of adenomas found at colonoscopy, the analysis was repeated using life expectancy as a timescale. In a multivariate analysis, the only independent risk factor for first adenoma recurrence was having more than two adenomas (OR=1.88; 95% CI 1.35-2.63; p<0.001). The difference in age at diagnosis disappeared at first recurrence (*figure 3*) when stratified for this predicting factor. Thus, having more than two adenomas was associated with a shorter interval to the first recurrence, as shown in *figure 2*.

Risk factors for metachronous adenoma at second and third surveillance

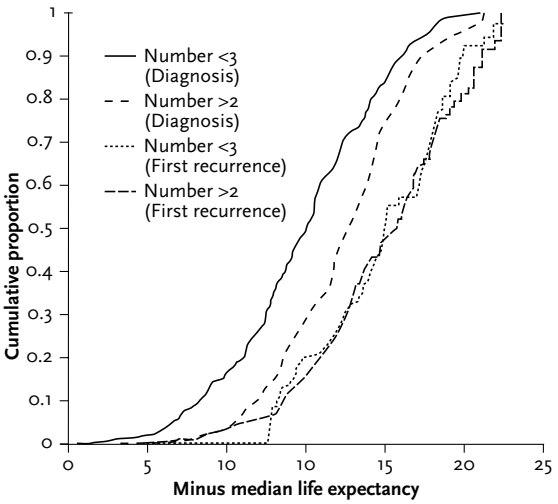
Follow-up after adenoma development of adenomas at first surveillance was available in 147 patients, 40 of whom could be studied after development of their second adenoma. When analysed by using either adenoma interval or life expectancy as a timescale, sex, age at, and characteristics of first or second recurrent disease were not found to be risk factors for the incidence of second and third metachronous adenomas. Again, cumulative proportions of 30% were reached after about five years, and 50% after about eight years.

Figure 2. *First metachronous adenoma stratified for number of adenomas at diagnosis: Kaplan-Meier curve*



Incidence of first metachronous adenoma stratified for number of adenomas at diagnosis over the years after diagnosis. Patients who had more than two adenomas will have their first recurrence earlier (p<0.001).

Figure 3. *First metachronous adenoma stratified for number of adenomas at diagnosis: life expectancy scale*



Incidence of adenoma at diagnosis and first adenoma recurrence, stratified for number of lesions at diagnosis, during lifetime till death. Age at diagnosis depends on the number of adenomas, but at first recurrence all patients have the same age.

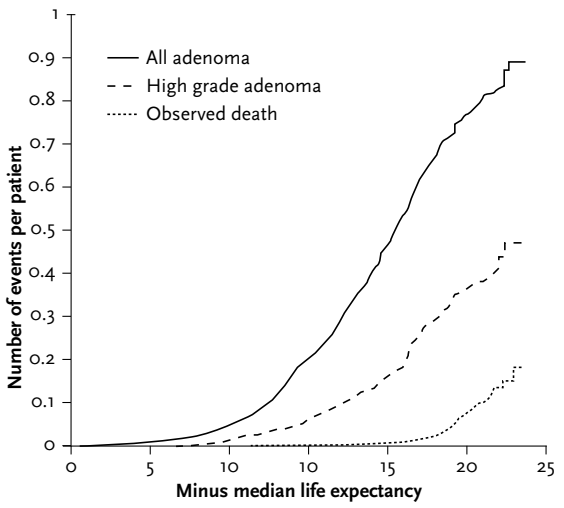
Prevalence of adenoma with high-grade dysplasia

Multivariate Cox regression analysis identified age (HR=1.05; 95% CI 1.03-1.07; p<0.001) and high-grade dysplasia in the preceding adenoma (HR=1.73; 95% CI 1.13-2.64; p=0.012) as independent risk factors for the development of adenomas with high-grade dysplasia after combining all of the time intervals between positive colonoscopies. Analysis using life expectancy as a timescale, stratified for rank number of recurrence, confirmed that high-grade dysplasia was an independent predictor of the development of recurrent high-grade dysplasia (OR=1.81; 95% CI 1.20-2.72; p=0.004). When stratifying for high- and low-grade dysplasia in all consecutive adenomas and their metachronous lesions, the prevalence of adenomas with high-grade dysplasia proved to be independent of the length of the interval between colonoscopies.

Overall natural course of colorectal adenomas

All data were used to graphically depict the course of the incidence of colorectal adenomas, both in total and of those with high-grade dysplasia (*figure 4*). A patient was estimated to experience 3.6 positive colonoscopies on average, baseline colonoscopy included. Of the 3.6 positive colonoscopies, 1.9 concerned adenomas with high-grade dysplasia.

Figure 4. *Cumulative incidence of total number of adenomas and of adenomas with high-grade dysplasia*



Overall natural course of repetitive incidence of total number of adenomas and of adenomas with high-grade dysplasia till observed death on a life expectancy scale.

DISCUSSION

Numerous studies on the risk of development of metachronous colorectal adenomas have been published so far.[4,6,15,20,26-30] However, our study is quite different from previous studies due to a median follow-up of 85 months and in a great majority of patients the follow-up intervals were determined according to the national guidelines. This follow-up is longer than in most other studies with follow-up periods ranging from 18-47 months.[15,26,27] The long follow-up allowed us to analyse not only the influence of potential risk factors on first surveillance, but also on second and third metachronous adenoma.

The advantage of using life expectancy as a timescale in the analyses is that it allows for proper adjustment for differences in sex, age and birth cohort at the start of follow-up among the patients. This enables a comparison of the incidence of events at the same phase of life, and makes graphical depiction of the natural course of the disease possible. As a result, the estimate can be made that on average an adenoma patient will be confronted with more than three positive colonoscopies during his or her lifetime, of which nearly two will show adenomas with high-grade dysplasia.

Our analysis showed that after polypectomy for adenomatous polyps, adenomas developed in more than 50% of the patients. In 20% of patients, advanced neoplasia was found during a median follow-up of seven years. This high frequency of metachronous adenomas is in accordance with findings of other studies.[6,20,31] Only two of our patients (0.7%) developed a carcinoma, which is comparable with other results.[15]

Multivariate analysis in our patient group showed male sex, three or more adenomas and high-grade dysplasia to be significant risk factors for any metachronous adenomas. Older age and high-grade dysplasia were identified as risk factors for development of high-grade dysplasia neoplasia. When these factors were analysed using life expectancy as a timescale, only the presence of three or more adenomas proved to be an independent predictor of adenoma development. No additional risk factor was found for any further new lesions. This method of analysis demonstrated that high-grade dysplasia in a preceding adenoma formed a risk for a next advanced neoplastic lesion. Other studies have also identified these risk factors.[4,6,15,20,26-30] Number, size, proximal location, tubulovillous features and age have all been identified as predictors of metachronous adenomas.[4,26-29,32] A pooled multivariate analysis and a more recent systematic literature review found older age, male sex, number, size and proximal location to be associated with metachronous (advanced) neoplasia.[15,33] In a recent Dutch study, data of 2990 patients who underwent surveillance colonoscopies in ten hospitals were analysed. They found these same risk factors, but also that adenomas with more than 75% villous histology, size >1 cm and proximal location predicted recurrence of high-risk adenoma.[34] In contrast to our study, high-grade dysplasia was not identified as a risk factor for first recurrence.

The studies mentioned above provided the basis for practical recommendations on surveillance. The Dutch study forms the basis of a scoring table in the newest Dutch guidelines just published.[34,35] But they are all mainly based on baseline characteristics and not on further findings during longer follow-up. International guidelines are summarised in *table 2a* and the recently published Dutch guidelines are added in *table 2b*.[5,16,35-38]

Our analysis on second and third adenoma development revealed no risk factors at all. The fact that three or more adenomas found at baseline colonoscopy was associated with a shorter interval to the first recurrence, but not to any further metachronous adenomas, is worth noting. Apparently, patients who present later for their first examination are at older age and more often men, and have more adenomas with a higher prevalence of high-grade dysplasia. It appears that patients with more than two adenomas have their first adenoma develop earlier (30% after 2.5 years) compared with the rest of the study group (30% after five years), and that the metachronous adenomas more often contain high-grade dysplasia. However, at the time of finding the first metachronous adenoma, the age difference has disappeared. Interestingly, from that moment on recurrence intervals are about the same regardless of any risk factors. Hence, our

Table 2a. *Overview of guidelines for surveillance after polypectomy*

Guidelines (ref)	Criteria: if..	Interval recommended
American[37,38]	<3 adenomas and tubular and LGD and <1cm	5-10 years
	3-10 adenomas or any advanced feature	3 years
European [5]	<3 and <1 cm and tubular and LGD and no family history[1]	5 years
	All other	3 years
German[5]	Tubular and <1 cm and no family history[1]	10 years
	All other	3 years
UK[5,36]	<3 adenomas and <1 cm	5 years
	3-4 adenomas or >1 cm	3 years
	All other	1 years
Dutch 2002[16]	<3 adenomas	6 years
	>2 adenomas	3 years

LGD= low-grade dysplasia; [1]no first-degree relatives with colorectal cancer.

Table 2b. *Dutch guideline for surveillance after polypectomy 2013*

Adenoma characteristics	Value	Score
Number of adenomas	0-1	0
	2-4 >5	1
		2
At least 1 adenoma >1 cm	No	0
	Yes	1
At least 1 villous adenoma (>75% villous features)	No	0
	Yes	1
At least 1 proximal adenoma	No	0
	Yes	1

Total score at index colonoscopy	Interval recommended
0	No surveillance
1-2	5 years
3-5	3 years
Total score at surveillance colonoscopy	
0	5 years
1-2	5 years
3-5	3 years

study shows that the period to second metachronous adenoma development no longer depends on the number of adenomas at subsequent investigations. When patients were stratified for high- and low-grade dysplasia, a significant relation was found between high-grade dysplasia at a preceding positive examination and high-grade dysplastic lesions during further follow-up, but again, this did not depend on the interval between colonoscopies.

A few studies have been published in which risk of metachronous adenoma was assessed by including the findings of follow-up colonoscopies.[39-41] They divided patients into groups with low- and high-risk findings. Extending surveillance intervals for low-risk groups may be considered.[39,40]

One of the limitations of our study is that no information was available on the precise conditions under which the colonoscopies were performed apart from documented caecal intubation. Factors such as withdrawal time and cleanliness of the colon, which are known to influence the detection rate of neoplastic lesions, had not been systematically recorded.[42,43] During our study, the bowel preparation protocol was not changed over time and cleanliness of the colon was overall good, as was shown in two studies in our centre.[44,45]

Another limitation is that no data were available on patients' family histories and that a small number of follow-up endoscopies were performed for diagnostic purposes. Finally, the graphs and recommendations from this study in the Dutch population may possibly not be extrapolated to other populations.

In summary, our study shows that the number of adenomas at baseline colonoscopy is the primary determinant and independent risk factor for early metachronous adenoma development. The number of adenomas was associated with high-grade dysplasia, proximal location and male sex. However, all these characteristics were significantly associated with advanced age at presentation. Therefore, our statistical analysis was properly adjusted for age, sex and birth cohort by using life expectancy as a timescale. Our long follow-up period and the subsequent results of several consecutive examinations gave us the opportunity to analyse the time elapsed between the development of adenomas. Our graphs could be used to abstract the interval time in future follow-up guidelines. When, for example, an adenoma recurrence proportion of 30% is accepted, an interval of approximately 2.5 years could be implemented when more than two adenomas were found at the first positive colonoscopy. For the second surveillance endoscopy, however, a time interval of five years would be appropriate for all patients, irrespective of the initial number of adenomas. Only the prevalence of advanced neoplasia will be higher in patients with preceding high-grade dysplasia and does not depend on the interval. To conclude, we believe our results, which are based on a long follow-up period and consecutive findings, will be useful when updating guidelines.

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CASE REPORT

Unexpected diagnosis of visceral leishmaniasis in a patient presenting with an infected ICD lead

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ABSTRACT

Visceral leishmaniasis (VL) is a rare disease in Western countries. Infection with *Leishmania* parasites usually remains asymptomatic, but may cause significant disease in children and immunocompromised adults in endemic areas. Here, we report a case of sporadic VL caused by *Leishmania infantum* in an immunocompetent patient who had visited Southern France one year ago and presented with implantable cardioverter defibrillator (ICD) lead infection.

KEYWORDS

Sporadic visceral leishmaniasis, immunocompetent, Mediterranean

What was known on this topic?
Visceral leishmaniasis is a common disease in Southern and Western Asia, Ethiopia, Sudan and Brazil. It is mostly seen in children and in immunocompromised patients.

What does this case add?
Visceral leishmaniasis can be underlying or concurrent with a bacterial infection and should also be considered in patients who are immunocompetent and have a travel history restricted to Mediterranean countries.

INTRODUCTION

Visceral leishmaniasis (VL) is caused by the protozoan *Leishmania donovani* (South Asia and East Africa) or *Leishmania infantum* (Mediterranean basin, Middle East, Western Asia and Brazil) and is transmitted by sand flies (genus Phlebotomus). *L. infantum* has a zoonotic form of transmission with the domestic dog as main reservoir. Infections usually remain asymptomatic with an estimated 30-100 asymptomatic infections for every symptomatic case in the Mediterranean region.[1] Until recently, endemic VL in Southern Europe occurred mainly in young children. With increased incidence of immunosuppression due to HIV infection, transplantation and chemotherapy, about half the cases are now in adults.[2] Sporadic VL may occur in non-indigenous people of any age who have visited endemic areas. The incubation period may be lengthy and ranges from weeks to years. Symptoms include malaise, prolonged irregular fever and weight loss with hypersplenism. Anaemia may develop due to haemolysis, bone marrow suppression and splenic sequestration. Darkening of the skin is typically found in India, but not in Europe (the Hindi name, *kala-azar,* means 'black fever'). Without treatment, VL is nearly always lethal due to infectious and haemorrhagic complications.[3] However, with liposomal amphotericin B treatment or pentavalent antimonials, high cure rates are reached.[4] Here, we report a case of VL in an immunocompetent patient with a seemingly insignificant travel history, who presented with a bacterial infection.

CASE REPORT

A 69-year-old autochthonous Dutch patient presented with complaints of malaise, rigors, night sweats and weight loss over the past three weeks. Medical history included diabetes mellitus and a myocardial infarction with cardiac

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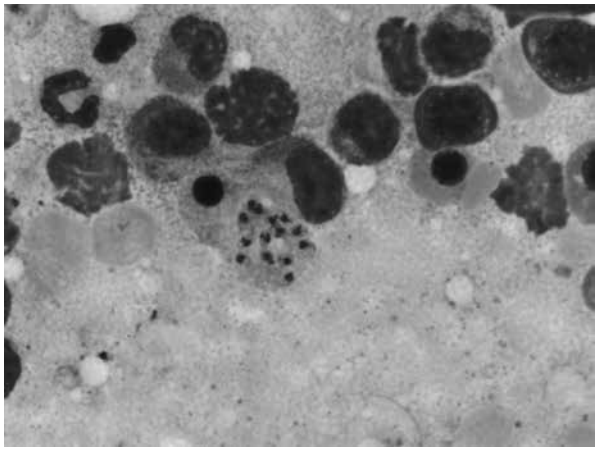
arrest, after which percutaneous transluminal coronary angioplasty (PTCA) was performed and an ICD was placed. History was otherwise unremarkable and travel history did not include visits to tropical areas. Physical examination revealed a pale man with a diastolic heart murmur and splenomegaly. No rash or enlarged lymph nodes were observed. Laboratory analysis showed a pancytopenia, with haemoglobin 5.8 mmol/l, mean corpuscular volume 84 fl, reticulocyte count 240 x 10^9/l, thrombocytes 133 x 10^9/l and leukocytes 1.7 x 10^9/l. Furthermore, non-immune haemolysis was observed with 35% elliptocytes in the blood smear. Due to suspicion of endocarditis, a transoesophageal echocardiography was performed which demonstrated vegetations on the ICD lead. Blood cultures were positive for *S. hominis* and *S. epidermidis*. He was treated with flucloxacillin and the ICD lead, from which *S. hominis, S. epidermidis* as well as proprionibacterium were cultured, was removed.

Despite appropriate treatment and repetitively negative blood cultures, he continued to suffer from spiking fever, profuse perspiration, weight loss and general malaise. Blood tests showed persistent pancytopenia with haemolysis.

Additional diagnostic tests were performed. Recent infection with cytomegalovirus, Epstein-Barr virus, parvovirus, or toxoplasma could be excluded by serological tests. Enzyme immunoassay for HIV-1 and -2 was negative. A positron emission tomography (PET) scan revealed increased uptake in bone marrow and spleen. A bone marrow biopsy did not show a haematological malignancy. A more detailed travel history revealed regular visits, the last one nearly a year ago, to Southern France, the Cévennes region. He recalled that in this region dogs are advised to wear insecticidal collars to protect against sand fly bites. This comment led us to suspect VL. Bone marrow samples were reviewed and *Leishmania* species amastigotes were identified (*figure 1*). *L. infantum* infection was confirmed with direct agglutination test and polymerase chain reaction. Treatment with liposomal amphotericin B for a total dose of 20 mg/kg was given, which resulted in immediate clinical improvement. At follow-up visits, no more periods of fever were reported, splenomegaly was reduced and leucocytes and thrombocytes had normalised. He still had a well-compensated non-immune haemolytic anaemia, which was ascribed to previously unknown hereditary elliptocytosis, which was also found in one of his two daughters.

Figure 1. *Bone marrow aspirate showing Leishmania species amastigotes*



DISCUSSION

We describe a case of sporadic VL caused by *L. infantum* in an immunocompetent autochthonous Dutch patient. Although leishmaniasis (*L. infantum)* is endemic in Mediterranean areas, cases of VL are relatively rare.[5] In the Netherlands, incidence of VL is estimated at 5-10 patients per year. However, exact incidence is unknown since there is no obligation to mention cases to Health Authorities.[6] In these sporadic VL patients the infection is contracted while visiting an endemic region, not seldom a long time ago.

Since the vector is not present in the Netherlands, there is no risk for local transmission.[6] However, due to climate change, the sand fly vector is increasingly found in more northern European regions. Therefore VL incidence in the Netherlands might increase in the next decades.[7]

In endemic countries many people are infected with *Leishmania* species, but only a few develop symptoms, predominantly children and immunocompromised individuals, most notably HIV patients.[7] Following initial infection, *Leishmania* parasites evade immune responses by several strategies, including neutralisation of complement factors, preventing release of macrophage superoxide, and suppression of induction of T lymphocytes, thereby surviving in host macrophages without causing symptoms. The mechanisms involved in parasite reactivation leading to the clinical syndrome of VL, in particular in relation to host immune status, are presently unknown.[8]

Remarkably, our patient was immunocompetent. Diabetes mellitus has not been recognised as a risk factor for VL. The relationship between infection of his ICD lead and reactivation of *L. infantum* is uncertain. Most likely, VL-induced immune suppression had made our patient susceptible for infections. Indeed, VL-associated morbidity and mortality is mostly driven by infectious complications.[9]

Liposomal amphotericin B at a total dose of 15-25 mg/kg is the reference treatment in the Mediterranean region with 90-98% efficacy.[2] A relapse in successfully treated patients occurs in 5% of patients.[8]

In conclusion, VL should be considered in patients with persisting fever, weight loss, splenomegaly and

pancytopenia, when more common diagnoses have been excluded and when there is a travel history to an endemic area. This also holds true for patients who are immunocompetent and for patients with a travel history restricted to the Mediterranean region, where *L. infantum* is endemic. As the incidence of leishmaniasis is expected to increase in Europe over the next decades and VL is usually lethal when untreated, increased awareness and early recognition by carefully taking the travel history are of utmost importance.

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PHOTO QUIZ

Looks can be deceiving

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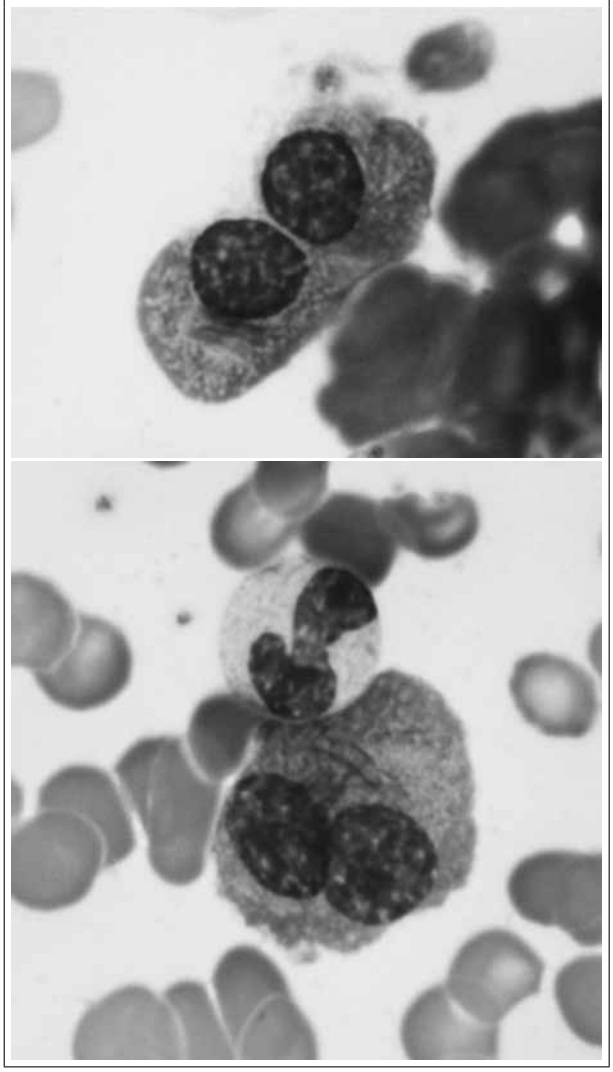
CASE REPORT

A 57-year-old man, with a 14-year history of IgA kappa monoclonal gammopathy of undetermined significance (MGUS), presented with anaemia, renal insufficiency and a rising serum IgA M protein. His laboratory results showed a haemoglobin of 6.3 mmol/l, thrombocyte count of 110 x 10^9/l, creatinine of 112 mmol/l and a IgA kappa M spike of 26 g/l. In *figure 1* the bone marrow aspirate is shown.

WHAT IS YOUR DIAGNOSIS ?

See page 153 for the answer to this photo quiz.

Figure 1. *Bone marrow aspirate*



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Netherlands
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PHOTO QUIZ

Shoulder pain after alcohol consumption

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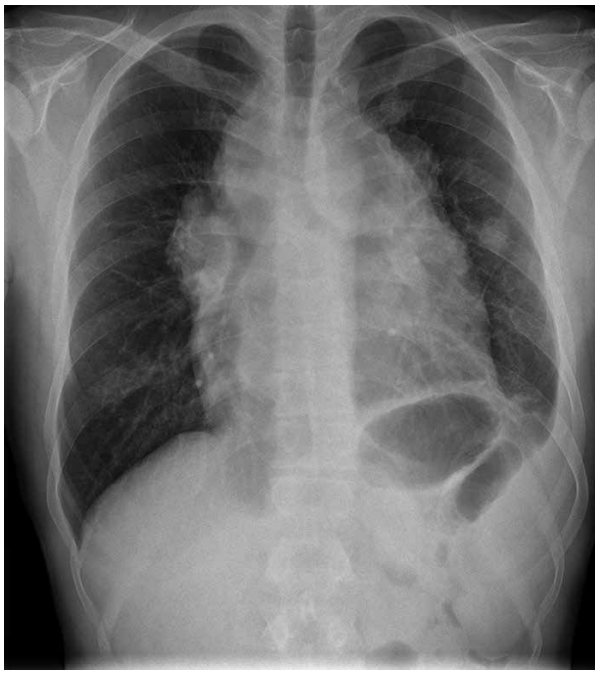
CASE REPORT

A 30-year-old man presented to our outpatient clinic because of intense pain in the left shoulder region related to consumption of alcoholic beverages, and an abnormal chest X-ray. He had stopped drinking alcoholic beverages in the last six months because of this pain. In addition he had weight loss, approximately 5 kg in the last couple of months, night sweats and a dry tickling cough. There was no relevant medical history.

The most important findings on physical examination were bilateral supraclavicular lymphadenopathy with an average diameter of 1 cm and a large palpable lymph node in his left axilla of 4 cm. Laboratory results showed erythrocyte sedimentation rate 49 mm/hour, haemoglobin 7.2 mmol/l, leukocytes 9.2 x 10^9/l, with lymphocytes 6%. Chest X-ray shows a widening of the superior and middle mediastinum with a solitary node in left upper lung lobe *(figure 1)*.

Figure 1. *Chest X-ray (posterior-anterior) shows a widening of the superior and middle mediastinum with a solitary node in upper left lung lobe*



WHAT IS YOUR DIAGNOSIS ?

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PHOTO QUIZ

A rare cause of an ST-elevation myocardial infarction

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CASE REPORT

A 49-year-old man was successfully resuscitated by terminating ventricular fibrillation with an electric shock. He was mechanically ventilated. The ECG showed that he had suffered from a semi-recent anterolateral myocardial infarction (*figure 1*).

Figure 1. *The ECG reveals a recent anterior STEMI with Q waves, ST elevations and negative T waves from V1 to V5*

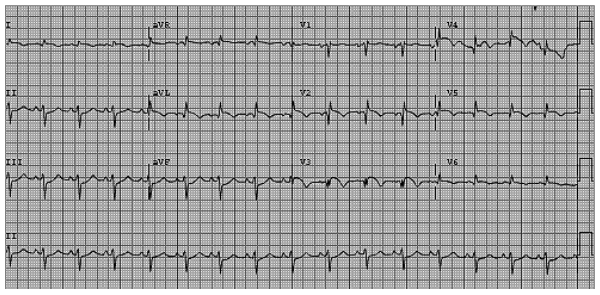


Figure 2. *TTE view demonstrates a large intrapericardial mass at the free left ventricular wall. The mass extends into the left atrium. The mass cannot be well delineated from the myocardium. LV = left ventricle; RV = right ventricle; M = mass*

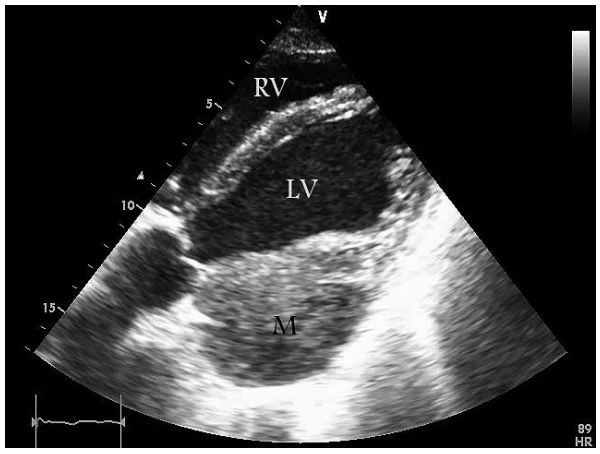
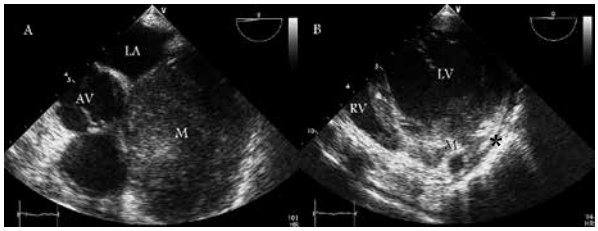


Figure 3. *Panel A: TEE image at 8° demonstrates the giant intrapericardial mass (M). Panel B: TEE transgastric view at 0° shows the giant mass (M) at the anterior free left ventricular wall. Note its inhomogeneous nature and a small amount of pericardial effusion (*). These findings are suggestive of a malignant intracardiac process. LV = left ventricle; RV = right ventricle; M = mass*



Laboratory results were as follows: haemoglobin 7.6 mmol/l, leucocytes 27.4 x 10^9/l, creatinine 64 µmol/l, electrolytes within normal limits, troponin I 0.84/µg/l and C-reactive protein 17 mg/l.

When his wife arrived at the Emergency Department a medical history was taken. There was no cardiac history. He had a history of nicotine and alcohol abuse. There was a weight loss of 7 kg over the last six months. He was fatigued but had never consulted his general physician. He was not taking any medication.

However, this information from the patient's wife could not be well integrated into the clinical history of a recent myocardial infarction. The echocardiography study revealed a giant mass at the left side of the heart (*figures 2* and *3*). The free left ventricular wall could not be well delineated from the intracardiac mass. His left ventricular function was severely diminished. There was a small pericardial effusion. What would be the cause of the myocardial infarction?

WHAT IS YOUR DIAGNOSIS ?

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Netherlands
The Journal of Medicine

PHOTO QUIZ

A cutaneous ulceration with pulmonary mass

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CASE REPORT

A 74-year-old man was admitted with a one-month history of haemoptysis, fever, cough, and 8 kg weight loss. He reported a four-year history of a cutaneous chest wall lesion, with previous empiric treatment but no diagnosis. Physical examination revealed a large, painful, deep ulceration with elevated erythematous-violaceous borders and a necrotic and haemorrhagic base on the left side of the back (*figure 1*). Chest radiography and computed tomography revealed an irregular cavitated consolidation in the right lung (*figure 2A and 2B*). The ulceration spread and progressed rapidly, despite administration of systemic broad-spectrum antibiotics and antifungal medication. Laboratory tests, including those for cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies (ANCA), were negative. Cutaneous lesion cultures were also sterile. The patient underwent skin and pulmonary biopsies. The skin lesion showed diffuse neutrophilic infiltration without angitis or granuloma. Histological findings of the pulmonary biopsy corresponded closely with those of the skin biopsy. Systemic treatment with prednisone led to improvement of the cutaneous and pulmonary lesions within four weeks.

Figure 1. *A large ulceration with elevated erythematous-violaceous borders and a necrotic and haemorrhagic base on the left side of the back*

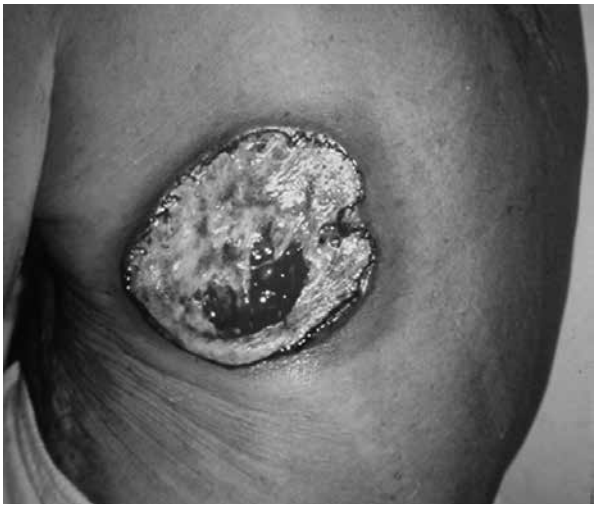
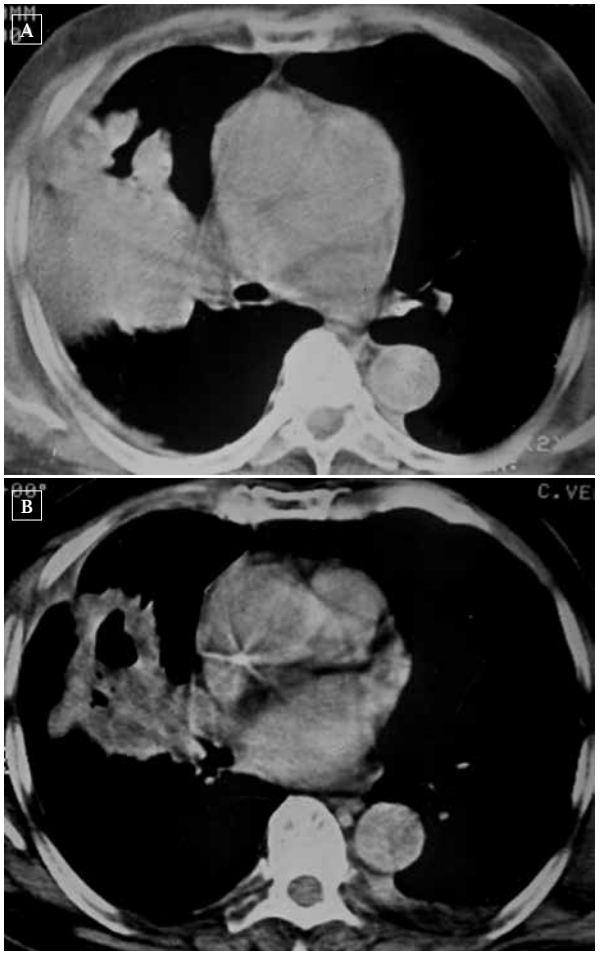


Figure 2. *Computed tomography scans (A and B) obtained at the level of the lower lobes showing an irregular cavitated opacity in the right lung*



WHAT IS YOUR DIAGNOSIS?

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ANSWER TO PHOTO QUIZ (PAGE 149)

LOOKS CAN BE DECEIVING

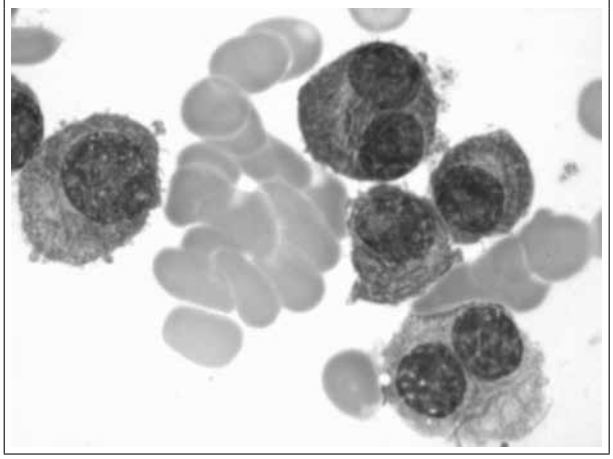
DIAGNOSIS

The bone marrow aspirate contained 50% plasma cells with the striking presence of abundant thick as well as slender Auer rod-like inclusions (*figure 1 and 2*) in most of those cells. Many looked like 'faggot cells' with a large number of rods. Less than 10% of the plasma cells had multinuclear forms. Otherwise, the marrow was normocellular and contained normal counts of white and red cell lines as well as megakaryocytes. Immunophenotyping of the aspirate revealed a cytoplasmatic-IgA+, cytoplasmatic-kappa+, CD38+, and CD138+ population. Trephine biopsy showed 75% CD138 and CD20 positive cells, which were kappa positive, consistent with the diagnosis of multiple myeloma.

Auer rods and faggot cells (cells containing multiple Auer rods which appear like a bundle of sticks) are usually associated with acute myeloid leukaemia, and considered pathognomonic for acute promyelocyte leukaemia (APL). However, in this case, the rods appeared in plasma cells and a diagnosis of symptomatic multiple myeloma was made.

Auer-like inclusions or pseudo-Auer rods have very rarely been reported in malignant plasma cells.[1,2] They should not be confused with APL-associated faggot cells. When in doubt, immunophenotyping can be helpful. The pathophysiology of these inclusions has not been unravelled. It has been suggested that they consist of active lysosomal plasma cell enzymes. The prognostic value of this morphological variant is unclear due to rarity of the cases.[1]

Figure 2. *Bone marrow aspirate*



The patient was considered unfit for intensive treatment due to comorbidities, and was started on melphalan, bortezomib, and prednisone. Unfortunately he was refractory to four cycles and has started second-line therapy with lenalidomide/dexamethasone.

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ANSWER TO PHOTO QUIZ (PAGE 150)

SHOULDER PAIN AFTER ALCOHOL CONSUMPTION

DIAGNOSIS

The differential diagnosis of a mediastinal mass, specifically in the superior and middle mediastinum, is a thymoma, malignant lymphoma/Hodgkin's disease, germ cell tumour, goitre, pericardial cyst or bronchogenic cyst. Furthermore a widened mediastinum can also be observed with sarcoidosis, mostly concentrated around the lung hilus.

The CT demonstrated extensive axillary, mediastinal and intraperitoneal lymphadenopathy, also splenomegaly was observed. Pathological examination of the left axillary lymph node revealed a classical Hodgkin's lymphoma with the characteristic histopathological finding of Reed-Sternberg cells (CD30 positive). Although bone marrow investigation showed no abnormalities, he was staged as 4B (Ann Arbor) because of the intrapulmonary abnormalities. Treatment with chemotherapy, doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) cycles was started.

His initial presentation with alcohol-induced shoulder pain is interesting since this was reported in the 1950-60s to be an anamnestic clue for specific types of malignancies. In 1950 Hoster was the first to describe that some patients with Hodgkin's disease experience pain at the site of disease if they drink alcohol.[1] The pain is of sudden onset, usually occurs 5-15 minutes after ingestion of even small amounts of alcohol and is sometimes of sufficient severity to induce patients to stop drinking alcoholic beverages. Treatment of Hodgkin's disease often abolished this phenomenon.

In an extensive survey Brewin reported that alcohol pain could occur in Hodgkin's disease but also in other malignant diseases, and occasionally in non-malignant conditions.[2] In this survey of 1060 patients with neoplasms, 155 patients showed alcohol intolerance. Of 1060 patients, 360 (34%) had Hodgkin's disease and 60 of these patients (17%) had alcohol pain. The remaining 95 patients with alcohol intolerance were diagnosed with cervical cancer (16 patients), reticulum-cell carcinoma (11 patients), lymphosarcoma (11 patients), lung cancer (9 patients), bladder cancer (6 patients), squamous carcinoma of the mouth (6 patients), breast cancer (4 patients), uterine cancer (3 patients), anaplastic lymphoid sarcoma (1 patient) and lymphoma (1 patient). In 1967 Brewin described that alcohol intolerance was also a phenomenon in women with cervical, uterine or ovary cancer, where alcohol intolerance manifested predominantly in patients with cervical cancer.[3] James *et al.* and Atkinson *et aI.* reported alcohol pain incidences of 7 and 17%, respectively, in Hodgkin's disease patients.[4,5] The latter group also reported that alcohol pain in Hodgkin's disease was even associated with at least one unfavourable prognostic indicator in a small number of subjects (n=27), but did not affect overall survival in this small group.[4]

The exact mechanism of alcohol-induced pain is not clear, the most plausible theoretical explanation to date is that alcohol induces a sudden intense vasocongestion in the neoplastic tissue resulting in capsular stretch inducing the pain.

Although still not completely understood, alcohol pain could be an important anamnestic clue for malignancies, in particular Hodgkin's disease, in patients with unappreciated complaints.

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ANSWER TO PHOTO QUIZ (PAGE 151)

A RARE CAUSE OF AN ST-ELEVATION MYOCARDIAL INFARCTION

DIAGNOSIS

Given the history of loss of weight, fatigue and an inhomogeneous intracardiac mass, suspicion of a malignant tumour, with dismal prognosis, arose. An axial computed tomography scan of the chest, abdomen and brain confirmed the intracardiac mass and was unable to detect other tumorous masses. Nonetheless, it was thought to be good clinical practice to obtain histology of the lesion to establish a diagnosis in order to determine the treatment options. He was subsequently transferred to a university hospital.

Coronary angiography demonstrated severe obstruction of the entire left anterior descending artery due to external compression. A needle biopsy was performed. The histopathology diagnosed a malignant poorly differentiated tumour. Unfortunately, the aspirated specimen contained too much necrotic tissue to allow an adequate immunohistochemical typing and identification. Once the diagnosis of a giant malignant intracardiac tumour was made, the patient was considered incurable as complete surgical resection of the mass was impossible. The needle biopsy was not repeated because there were no further therapeutic consequences. He died at day 10 due to heart failure and untreatable ventricular arrhythmias. The family refused an autopsy.

The differential diagnosis of an intracardiac mass in this case was challenging and included benign and malignant primary cardiac tumours, metastatic tumours, intracavitary thrombus, chronic infective or systemic inflammatory processes and a pseudoaneursym with cloth formation in its cavity. This last diagnosis was rejected because echocardiography was unable to detect discontinuity of the free left atrial wall.

In differentiating the nature of an intracardiac mass, echocardiographic features may be helpful. The inhomogeneous consistency was in favour of a malignant process and there was a small pericardial effusion to support this diagnosis. The location of the mass at the free lateral ventricular wall was not typical for a thrombus.

The reported incidence of primary cardiac tumours among the general population varies between 0.001% and 0.03% in most autopsy series and 25% of these tumours are malignant. Malignant tumours metastasised to the heart outnumber primary malignant cardiac tumours by at least a 30-to-1 ratio.[1,2]

To the best of our knowledge, only three previous reports have described a myocardial infarction caused by a cardiac sarcoma – the most common primary malignant cardiac tumour – as the first clinical presentation. A case of a fatal cardiac infarction caused by an intimal sarcoma originating from a coronary artery has been reported.[3] Myocardial infarction due to an embolic event as consequence of the presence of an atrial sarcoma has been described twice.[4,5]

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ANSWER TO PHOTO QUIZ (PAGE 152)

A CUTANEOUS ULCERATION WITH PULMONARY MASS

DIAGNOSIS

The aggressive nature of the patient's ulcers, in combination with the negative findings of laboratory tests, cultures for bacteria and fungi, and histopathological examination, allowed the diagnosis of pyoderma gangrenosum (PG).

PG is a chronic inflammatory disease of unknown aetiology, characterised by neutrophilic infiltration of skin and lung tissues.[1,2] Its cutaneous manifestation is characterised clinically by erythematous-violaceous nodular lesions or pustules that progress and enlarge rapidly to painful ulcers of variable size, with irregular, loose borders and necrotic and haemorrhagic bases, preferentially located on the lower limbs.[3,4] The pathogenesis of PG remains unclear, but may involve derangement of immunity and/or neutrophil function.[1]

PG has been reported in association with various systemic diseases involving basic immunological disorders, such as inflammatory bowel disease (ulcerative colitis, Crohn's disease), polyarthritis, vasculitis, lymphoma, paraproteinaemia, leukaemia, rheumatoid arthritis, gammopathies, multiple myeloma, and active chronic hepatitis.[1-4]

Although PG is basically considered to be a dermatological disease, its clinical appearance has some systemic aspects.[2] Extracutaneous manifestations of PG are uncommon and have been reported in the bones, lungs, trachea and bronchi, liver, heart, pancreas, spleen, kidneys, and central nervous system.[3] Although systemic involvement is rare in PG, the lungs are the most commonly affected organs.[4] The main clinical manifestations in the lungs are solitary or multiple pulmonary nodules or masses, with or without evidence of central necrosis and cavitation, pleural effusion, and infiltration. The lungs of patients with PG also show marked intra-alveolar neutrophilic infiltration.[1-4] Skin biopsy is essential for diagnostic confirmation. Histological examination basically reveal aseptic inflammatory neutrophilic infiltrates.[4]

The differential diagnosis of PG primarily involves consideration of Wegener's granulomatosis, which can be associated with similar skin lesions and systemic involvement. The absence of upper respiratory tract involvement or kidney alteration, laboratory findings (cytoplasmic and perinuclear ANCA negativity), and pathological findings of tracheal and skin lesions ruled out Wegener's granulomatosis in our case.[2,4]

Steroid therapy is considered to be the first choice to control the systemic manifestations of PG, especially the pulmonary form.[2,4]

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SPECIAL ARTICLE

Practice of bridging anticoagulation: guideline adherence and risk factors for bleeding

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ABSTRACT

Background: Perioperative bridging with low-molecular-weight heparins (LMWH) is applied to minimise the risk of thromboembolism (TE). Guidelines characterise patients at risk and strategies to be followed. We assessed guideline adherence in bridging episodes and identified possible risk factors for bleeding in a retrospective cohort study.

Methods: We searched the electronic patient data system of the Maastricht anticoagulation service, the Netherlands. We identified 181 patients on chronic anticoagulation who underwent surgery (222 procedures) and were bridged with LMWH. Guideline adherence was defined in terms of the relation between TE risk and the dose of LMWH administered, the bleeding risk of the procedure and the duration of postprocedural administration of LMWH. Logistic regression was used to identify risk factors for bleeding.

Results: Of all low TE risk patients (n=102), 84.3% were treated with therapeutic doses of LMWH. The median duration of postprocedural LMWH administration was eight days. The 30-day incidence of major bleeding in the entire group (n=222) was 11.3%. Two patients (0.90%) experienced a deep venous thrombosis. Creatinine clearance ≤40 ml/min (odds ratio (OR) 5.03, 95% confidence interval (CI) 1.25 to 20.26) and dental procedures (OR 3.32, 95% CI 1.22 to 9.04) were independent predictors for total bleeding.

Conclusion: Guideline adherence was low, leading to prolonged bridging procedures, excess treatment of patients and high bleeding rates. The majority of patients had a low thromboembolic risk profile or underwent low-risk procedures. For patients with decreased creatinine clearance, reduced doses of LMWH should be considered to reduce bleeding risk.

KEYWORDS

Guideline adherence, bleeding, thrombosis, anticoagulants, risk factors for bleeding

INTRODUCTION

Perioperative interruption of chronic anticoagulation harbours the risk of thromboembolism (TE). To minimise the risk of TE during the anticoagulant-free interval, bridging therapy with low-molecular-weight heparins (LMWH) is applied. This introduces the risk of bleeding. Vitamin K antagonists (VKA) are administered to patients at increased risk of a venous or arterial TE due to, for instance, venous thromboembolism, atrial fibrillation, mechanical heart valves, or stroke. According to current guidelines, LMWH or unfractionated heparin (UFH) in therapeutic dosages is the preferred anticoagulant for high TE risk patients undergoing high bleeding risk surgery. For patients with an intermediate TE risk profile two options are available: therapeutic or prophylactic dosages of LMWH. For patients at low TE risk again two options are available: prophylactic dosages or interruption of VKA without LMWH or UFH. In low bleeding risk procedures VKA should not be interrupted. The perioperative administration of UFH or LMWH as a part of bridging therapy possibly leads to increased bleeding risk associated with sometimes severe consequences such as intracranial bleeding with major disability or even death as a result.[1-4] Although guidelines characterise patients at risk and advise on strategies to be followed, the application of bridging therapy is often guideline discordant. Literature reveals that a wide range of approaches to bridging anticoagulation are in use, possibly due to unfamiliarity with the current guidelines and the weak evidence on which they are based.[5,6] Evidence from randomised trials

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is lacking, probably because ethical issues might arise during the design of such a study; available evidence is therefore mainly based on observational studies. The incidence of postoperative total bleeding ranges from 4.1 to 25% in populations subject to diverse bridging regimes undergoing different surgical interventions.[4,7-9] The incidence of TE ranges from 0 to 2.6% in different studies.[3,4,10-13] Apart from improvement of adherence to guidelines there is a need for defining patient and procedure-related characteristics which might fine-tune the bridging strategy and thereby decrease the incidence of periprocedural bleeding and TE. Until now, renal insufficiency,[1,14] $CHADS_2$ (a composite score of congestive heart failure, hypertension, age, diabetes and stroke),[8,9,13] mitral valve replacement,[4,15,16] thrombocytopenia,[8,16] LMWH administration within 24 hours after the procedure,[16,17] increasing age,[7,13] and total duration of periprocedural heparin use[18] are the only consistent risk factors for bleeding. Baseline INR in bridging groups is not associated with postoperative bleeding in different studies.[7,19] It is still unclear if the application of bridging therapy results in decreased TE risk when compared with VKA cessation alone or VKA continuation without the administration of LMWH.[20]

Our primary goal was to delineate the features of bridging strategies applied in the region around Maastricht, the Netherlands. We intended to assess guideline adherence and to document the incidence of bridging-related bleeding and TE. The secondary goal was to identify possible risk factors for bleeding during bridging therapy, both patient-related risk factors and risk factors associated with the bridging strategy itself.

METHODS

Cohort

To determine guideline adherence and identify risk factors for major and total bleeding, we retrospectively searched the electronic patient data system of the Maastricht anticoagulation service for the interval of September 2010 until June 2012. This database contains data of approximately 4200 patients in relation to VKA therapy and bleeding complications. Additional medical information for these patients was retrieved from the patient database of the Maastricht University Medical Centre (MUMC+). Institutional review board approval was obtained (METC 11-4-140).

We identified 181 patients (222 procedures) on chronic anticoagulation who received bridging therapy. A broad definition of bridging therapy was used: any period of periprocedural cessation of VKA including the day of the intervention and administration of any dose of periprocedural LMWH or UFH. The following inclusion criteria were determined: 1) participants were bridged as defined above and 2) were on chronic VKA treatment, initiated more than three months ago. Participants, who had 1) additional surgery within 30 days, 2) underwent an emergency procedure, or 3) yielded inconsistent data, (i.e. contradictory information was found in the different databases) were excluded. We sought to report our study according to the recommendations for reporting studies in periprocedural antithrombotic and bridging therapy issued by the ISTH.[21]

Guideline adherence

We determined guideline adherence of bridging episodes; we ascertained the proportion of patients bridged according to the ACCP guidelines for perioperative management of antithrombotic therapy 2008.[22] These guidelines are officially adopted and propagated in the MUMC+. For surgical bleeding risk classification we made use of a two-tier distribution in our descriptive analyses; dental procedures, (extraction of 1-3 teeth, implant placement, surgical extraction of wisdom teeth, surgical root canal treatment, incision of an abscess, and dental hygiene treatment), cataract surgery, small dermatological interventions, and all other procedures with local anticoagulant options were considered low bleeding risk procedures making it possible to continue VKA treatment. All other procedures were qualified as high bleeding risk procedures and therefore warranted bridging anticoagulation according to ACCP guidelines, providing elevated TE risk was established in the patient. Arterial and venous TE risks were defined as low, intermediate, or high. TE risk in general was defined as a composite score of venous and arterial TE risk. A low, intermediate, or high arterial/venous TE risk was defined as a low, intermediate, or high composite risk respectively; in case of exposure to both an arterial and venous risk the highest score on either risk was expressed as the TE risk. The variable TE risk in general was composed to be able to estimate the combined effect of arterial and venous TE risk on the physician's decision to administer therapeutic doses of LMWH and on bleeding risk in our univariable and multivariable analyses. Guideline adherence was defined as low TE risk patients receiving prophylactic doses of LMWH postprocedurally and intermediate to high TE risk patients receiving prophylactic or therapeutic doses postprocedurally. Patients without prior surgical bleeding undergoing low-risk dental, cataract, or dermatological procedures should not be bridged; continuation of VKA is the preferred option, but for patients who have experienced prior surgical bleeding, bridging is indicated for these low-risk procedures. The period of postoperative administration of LMWH should not exceed seven days. We determined the proportion of all patients on long-term acenocoumarol or phenprocoumon therapy, treated within our institution, who received

postprocedural therapeutic doses of LMWH. In the literature this proportion ranges from 22 to 85% and is associated with major bleeding.[6]

Complications

We documented the incidence of perioperative total bleeding, major bleeding and TE from three days prior to until 30 days after the procedure. Major bleeding was defined according to the criteria used by the Federation of Dutch Thrombosis Services (FNT) as any bleeding resulting in death, any intracranial bleeding, and any bleeding that leads to transfusion of packed red cells and/or treatment in a hospital or joint bleeds; all other bleeding including haematomas is qualified as minor bleeding. Thromboembolic complications are defined as any objectively confirmed TE, and death caused by TE; myocardial infarction and acute coronary syndrome were excluded due to the difficulty of attributing these events to cardioembolism in the perioperative setting.[21]

Risk factors for bleeding

Primary outcomes were total and major bleeding. Due to the low number of cases we were unable to identify patient characteristics associated with the risk of TE. To assess bleeding risk of the procedure we used, in addition to the ACCP risk classification (low, high), the five-point scale as proposed by Jaffer *et al*. ranging from minimal bleeding risk (score 1) to critical risk (score 5).[6] This five-point scale was used in our univariable and multivariable analyses as an independent variable. Creatinine clearance was divided into three categories: >60, 41-60, and ≤40 ml/min for reasons of an approximate equal distribution of the obtained values among the categories. The postprocedural restart time of LMWH was estimated and rounded to 0.5 days (12 hours). The total duration of LMWH administration was calculated taking into account the intermediate period that the patient did not receive LMWH including the day of the intervention.

Statistical analysis

Descriptive statistics were used to determine patient and procedure characteristics. Continuous variables are reported as means, their standard deviations (SD), and median values; categorical data are presented as counts and percentages. To assess whether the bleeding risk of the intervention (score 1-5), TE risk (low, intermediate, or high), creatinine clearance (ml/min), or age (years) influenced the physician's decision to administer therapeutic dosages of LMWH postprocedurally, univariable and multivariable logistic regression were performed with therapeutic dosage of postprocedural LMWH as the outcome.

In order to identify risk factors for total and major bleeding, first univariable and subsequently multivariable logistic regression was applied. For our multivariable models with both total bleeding and major bleeding as outcomes, we selected the established risk factors age (years),[7,13] total duration of periprocedural heparin use (days),[18] and the variables associated in univariable analysis ($p<0.10$) with total bleeding: dental procedures (yes/no), TE risk (low, intermediate or high), and creatinine clearance (ml/min). In the univariable and multivariable analyses missing values were imputed; we opted for multiple imputations. Besides the original dataset five additional datasets were created using the Markov chain Monte Carlo method. The results of these six datasets were pooled. To assess the fitting of different models, Hosmer-Lemeshov and model chi-square statistic tests were performed. Risks are expressed as odds ratios (OR) and p-values for linear trends are presented. A two-sided p-value <0.05 was considered statistically significant. Data were analysed with SPSS version 19.0.0.

RESULTS

We were unable to classify 12 participants (12 procedures) in any TE risk category. According to the ACCP guidelines these patients were not indicated for VKA use; conditions such as thrombophilia without previous venous thromboembolism (VTE) and cardiomyopathy are not mentioned in the risk scheme.

Baseline characteristics

Baseline clinical characteristics are detailed in *table 1*. The average age was 70.3 years (standard deviation (SD) 11.4) and 59.0% were male. Arterial TE risk was the indication for VKA use in 190 patients (85.6%); low-risk atrial fibrillation (AF) with $CHADS_2$ scores 0-1 was the most prevalent condition in 67/190 patients (35.3%). VTE risk was present in 42 patients (18.9%); the most prevalent condition was VTE more than six months ago: 32/42 (76.2%). Ten patients had both an arterial and venous indication for VKA therapy. Creatinine clearance was decreased (≤60 ml/min) in 62/222 (27.9%) of the patients and in 62/126 (49.2%) of the measurements performed. In 96 (43.2%) patients no periprocedural creatinine clearance was determined.

Procedure characteristics

Procedure characteristics are detailed in *table 1*; 222 procedures were performed in 181 patients. In 62 (27.9%) of all cases, bridging therapy was applied for a procedure for which bridging was not indicated; all were low-risk dental, cataract, or dermatological interventions. A variety of inpatient and outpatient procedures were performed: dental procedures, gastroscopies, and colonoscopies were the most prevalent interventions (*table 2*). The majority (143, 64.4%) of all procedures were classified as minimal

Table 1. *Baseline and procedure characteristics, anticoagulation and complications*

Baseline characteristics		
Men		131 (59.0%)
Age (years)		70.3±11.4
Arterial TE risk (n=190)	High	42 (27.4%)
	Intermediate	56 (29.5%)
	Low	80 (42.1%)
	Not mentioned in ACCP/CBO guidelines	12 (6.3%)
Venous TE risk (n=42)	High	9 (21.4%)
	Intermediate	1 (2.4%)
	Low	32 (76.2%)
Creatinine clearance (n=222)	>60 ml/min	64 (28.8%)
	41-60 ml/min	42 (18.9%)
	≤40 ml/min	20 (9.0%)
	No measurement performed	96 (43.2%)
Procedure characteristics		
Bleeding risk procedures ACCP (n=222)	High	160 (72.1%)
	High bleeding risk procedure	157 (70.7%)
	Bleeding previous surgery	3 (1.4%)
	Low	62 (27.9%)
	Low bleeding risk procedure	62 (27.9%)
Bleeding risk 5-point scale (n=222)	Score 1	143 (64.4%)
	Score 2	33 (14.9%)
	Score 3	39 (17.6%)
	Score 4	7 (3.2%)
	Score 5	0 (0.0%)
Anticoagulation characteristics		
VKA (n=222)	Acenocoumarol Phenprocoumon	200 (90.1%) 22 (9.9%)
Vitamin K preprocedural (n=6)	Acenocoumarol Phenprocoumon	0 (0.0%) 6 (100%)
LMWH postprocedural (n=222)	Prophylactic	23 (10.4%)
	Therapeutic	199 (89.6%)
Stop time VKA (days)	Acenocoumarol Phenprocoumon	-3.4±1.6 Median: -3.0 -5.3±3.6 Median: -5.0
Restart time VKA postprocedural (days)	Acenocoumarol Phenprocoumon	1.4±3.3 Median: 0.0 2.1±8.0 Median: 0.0
Start time LMWH preprocedural (days)	Acenocoumarol Phenprocoumon	-3.2±1.7 Median: -3.0 -6.3±5.1 Median: -4.0
Stop time LMWH preprocedural (days)	Acenocoumarol Phenprocoumon	-0.9±0.5 Median: -1.0 -1.3±0.6 Median: -1.0
Restart time LMWH postprocedural (hours)	Acenocoumarol Phenprocoumon	19.3±9.9 Median: 24.0 19.3±9.5 Median: 12.0
Anticoagulation characteristics		
Stop time LMWH postprocedural (days)	Acenocoumarol Phenprocoumon	9.6±6.0 Median: 8.0 13.9±11.9 Median: 10.0
Total duration LMWH (days)	Acenocoumarol Phenprocoumon	11.2±6.2 Median: 8.5 17.6±13.8 Median: 13.0
INR day intervention	Acenocoumarol Phenprocoumon	1.1±0.1 1.2±0.2
Time INR>2 (days)	Acenocoumarol Phenprocoumon	8.7±6.9 Median: 7.0 11.8±10.5 Median: 8.0
Low TE risk and postprocedural LMWH dosage		
Low TE risk (n=102) and prophylactic dose		16 (15.7%)
Low TE risk (n=102) and therapeutic dose		86 (84.3%)
Complications		
Bleeding (n=44)	Transfusion	4 (1.8%)
	Hospital treatment	21 (9.5%)
	Minor	19 (8.6%)
TE (n=2)		2 (0.9%)

ACCP = American College of Chest Physicians; AF = atrial fibrillation; CBO = Centraal BegeleidingsOrgaan voor de intercollegiale toetsing; $CHADS_2$ = congestive heart failure, hypertension, age, diabetes and stroke(2); INR = international normalised ratio; LMWH = low-molecular-weight heparin; MHV = mechanical heart valve; TE = thromboembolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

bleeding risk procedures according to the Jaffer scale (score 1); no procedures were classified as critical risk (score 5), and only seven (3.2%) procedures were assessed as major bleeding risk (score 4). Of the participants, 17 underwent two procedures, seven participants underwent three, and two participants underwent four procedures.

Anticoagulation

Anticoagulation characteristics are detailed in *table 1*. The majority of the patients used acenocoumarol as oral anticoagulant: 200 (90.1 %), the remaining 22 (9.9%) used phenprocoumon. The median preoperative stop time of VKA was day -3 (mean -3.4, SD 1.6) and day -5 (mean -5.3, SD 3.6) for acenocoumarol and phenprocoumon, respectively. Vitamin K was used to reverse anticoagulation only in six patients (2.7%); all used phenprocoumon, a VKA with a relatively long half-life of 120-200 hours. Acenocoumarol was resumed after a median of 0 days (mean 1.4, SD 1.6); phenprocoumon was resumed after a median of 0 days (mean 2.1, SD 8.0). LMWH was used as bridging agent of first choice in all patients. The proportion of patients at low TE risk (n=102) treated with therapeutic doses of LMWH postprocedurally was 84.3% (n=86). We also explored periprocedural timing of LMWH administration; LMWH therapy was initiated at

Table 2. *Procedures performed (n=222)*

Gastrointestinal	
Endoscopy colon/duodenum with or without biopsy	26
Cholecystectomy	2
Abdominal surgery	7
Haemorrhoids	3
Colon polyp removal	1
Orthopaedic	
Total hip arthroplasty	5
Total knee arthroplasty	4
Intra-articular injections	3
Elbow/foot/shoulder surgery	3
Other	8
Urology	
Prostate biopsy	7
TUR prostate	4
Bladder cancer surgery	3
Brachytherapy	2
Kidney scope procedure	5
Cystoscopy with or without biopsy	2
Other	7
Dental	
Extractions	37
Implants	10
Dental hygiene treatment	1
Neurosurgical	
Surgery for spinal disc herniation	5
Lumbar puncture	1
Vascular	
Varices	2
Angioplasty/stent placement	2
Bypass surgery	1
Plastic	
Hand surgery	6
Dermatological procedure	8
Entropion surgery	3
Other	3
Interventional radiology	
Heart biopsy	2
Cardiac catheterisation	9
Other	2
Other	
ENT surgery	2
Neurolysis	11
Cataract	2
Umbilical or inguinal hernia	4
Breast cancer	4
Breast biopsy	6
Bronchoscopy with or without biopsy	4
Other	5

ENT = ear, nose and throat; TUR = transurethral resection of the prostate.

a median of 3 days (mean 3.2, SD 1.7) and a median of 4 days (mean 6.3, SD 5.1) before and stopped a median of 1 (mean 0.9, SD 0.5 and mean 1.3, SD 0.6) day prior to the planned procedure in acenocoumarol and phenprocoumon users, respectively. The median time of postoperative restart of LMWH therapy was 24 hours (mean 19.3, SD 9.9) and 12 hours (mean 19.3, SD 9.5) in acenocoumarol and phenprocoumon users, respectively. The median duration of postoperative LMWH administration was 8 days (mean 11.2, SD 6.2) and 13 days (mean: 17.6, SD 13.8) in acenocoumarol and phenprocoumon users, respectively. Of all patients undergoing bridging therapy, 199 (89.6%) were treated with therapeutic dosages of LMWH after the procedure.

Univariable logistic regression with postprocedural therapeutic dosage of LMWH as the outcome resulted in non-significant effects for all variables. No proof was found that the prescribing physician's decision to administer therapeutic dosages of LMWHs was influenced by age, TE risk, surgical bleeding risk, or creatinine clearance. Patients at high TE risk compared with low-risk patients had a non-significant higher risk of exposure to therapeutic doses (OR 4.22, 95% CI 0.93 to 19.24), p for linear trend=0.06. Patients with a creatinine clearance within the range of 41-60 ml/min compared with a clearance >60 ml/min had a non-significant lower risk of exposure to therapeutic doses (OR 0.43, 95% CI 0.10 to 1.82), p for linear trend=0.88. A high bleeding risk procedure (score 4) on the Jaffer scale compared with a procedure score of 1 resulted in a non-significant decreased risk of exposure to therapeutic doses of LMWH (OR 0.24, 95% CI 0.04 to 1.36), p for linear trend=0.11. Multivariable analyses including the aforementioned variables resulted in overall non-significant results. Patients at high TE risk compared with low risk had a borderline non-significant higher risk of exposure to therapeutic dosages after their intervention (OR 4.96, 95% CI 0.97 to 25.26), p for linear trend=0.05. Patients with a creatinine clearance within the range of 41-60 ml/min compared with clearance >60 ml/min had a non-significant lower risk of exposure to therapeutic doses (OR 0.38, 95% CI 0.08 to 1.81), p for trend=0.73. Finally, a bleeding risk score 4 compared with score 1 resulted in a non-significant decreased risk (OR 0.27, 95% CI 0.04 to 1.86), p for linear trend=0.23. The goodness of fit of the model was assessed, resulting in a p-value of 0.77 on the Hosmer-Lemeshov test and the model chi-square statistic resulted in a p-value of 0.75.

Complications

The 30-day incidence of total bleeding in the entire group of procedures performed was 44 (19.8%), the incidence of major bleeding 25 (11.3%); there were no deaths, no intracranial bleeding, four patients required a transfusion,

and 21 had to be treated in a hospital due to postoperative bleeding. Two patients (0.9%) experienced a deep venous thrombosis and recovered (*table 1*).

Risk factors for bleeding

Univariable logistic regression analysis revealed high versus low TE risk (OR 2.59, 95% CI 1.11 to 6.04), p for linear trend=0.03 and dental procedures (OR 2.98, 95% CI 1.45 to 6.13) as risk factors for total bleeding; all other results are non-significant. Creatinine clearance ≤40 versus >60 ml/min and intermediate versus low TE risk resulted in non-significant elevated risks: OR 2.35, 95% (CI 0.93 to 5.90), p for linear trend=0.07 and OR 1.83, 95% CI 0.77 to 4.33, respectively. To minimise the risk of reversed causality we excluded 18 cases in which VKA were stopped and LMWH administration due to total bleeding was prolonged; the initial significantly increased risk caused by the total duration of LMWH administration (result not shown) disappeared: (OR 0.94, 95% CI 0.86 to 1.03). After exclusion of the aforementioned 18 cases, dental procedures (OR 3.32, 95% CI 1.22 to 9.04) and creatinine clearance ≤40 versus >60 ml/min (OR 5.03, 95% CI 1.25 to 20.26), p for linear trend=0.02 were identified as independent predictors of total bleeding in a model completed with the variables age, duration of periprocedural use of LMWH, and TE risk. The Hosmer-Lemeshov test resulted in a p-value of 0.47 and the model chi-square statistic yielded a significant result: p=0.01.

Finally, we explored major bleeding. Univariable logistic regression revealed intermediate versus low TE risk as a risk factor (OR 3.40, 95% CI 1.17 to 9.93), p for linear trend=0.11. No further risk factors were identified. Our dataset contained only three high TE risk patients due to mitral valve replacements of which one experienced major bleeding; hospital treatment was necessary (OR 4.06, 95% CI 0.36 to 46.50). In multivariable analysis, using the same model, we again excluded the aforementioned 18 cases to avoid differential misclassification and no significant risk factors were identified. The model as a whole scored a p-value of 0.83 on the Hosmer-Lemeshov test with a p-value of 0.50 on the model chi-square statistic.

DISCUSSION

In our study we found that guideline adherence in bridging therapy in the region around Maastricht, the Netherlands is not optimal. The most striking finding is that 84.3% of all low TE risk patients were bridged with therapeutic doses of LMWH. Low TE risk does not warrant bridging therapy and certainly not with therapeutic doses of LMWH.[22] Furthermore, compared with other studies, we found high rates of total and major bleeding.[6,9,23,24] We were unable to find an association of this observed aggressive treatment with anticoagulants and the high bleeding rates, possibly due a lack of contrast in our population. Studies performed by Jaffer *et al.* and Robinson *et al.* identified postprocedural therapeutic doses of LMWH as a risk factor for bleeding.[6,11] In general, bridging therapy exposes the patient to additional risks, also including a risk of heparin-induced thrombocytopenia (HIT).[25] Interventions for which no bridging anticoagulation is indicated and VKA administration can simply be continued represented 27.9% of the total number of procedures performed in our cohort; a fairly high proportion. Possibly due to the fact that the majority of the participants were outpatients, the period of exposure to LMWH was much longer than necessary according to the ACCP guidelines; in outpatients rigidly performed INR testing is often not feasible.[26] Furthermore, due to a change in the anticoagulant regime in the outpatient setting the patient's compliance might be at risk; this might introduce an additional risk factor for bleeding or TE. Another possible explanation for prolonged LMWH administration might be the use of too low restart doses of VKA (i.e. the maintenance dose) instead of 1.5 to 2 times higher doses of acenocoumarol and phenprocoumon as advised in guidelines issued by the FNT.[27] Overall TE incidence was low and in concordance with some other studies;[6,9,23,24] no arterial TE occurred. We conclude that individual clinicians often do not act according to the current bridging guidelines; in the observed cohort the decision to administer therapeutic dosages of LMWH was not or barely influenced by surgical bleeding risk, TE risk, or renal insufficiency. Krahn *et al.* and Skolarus *et al.* report similar findings;[5,28] Gerson *et al.* on the other hand concluded that most people receiving bridging therapy were managed according to current society guidelines.[29] Possible explanations for non-adherence are the lack of familiarity with these guidelines, lack of awareness of the significance of consistent bridging practices, disagreement with the guidelines, and resistance to change.[30] It is also conceivable that physicians tend to over-treat patients because the threat of a TE is considered more severe than the threat of bleeding.[5]

Renal insufficiency appeared an independent predictor for total bleeding. Other studies support this finding;[1,14] the clearance of LMWH is primarily renal, the plasma half-life increases in patients with renal failure and dose reduction is advised in these patients following the Cockroft-Gault formula.[8,31] As far as we know only one study performed by Hammerstingl reported high TE risk as a risk factor for perioperative bleeding.[8] Possibly confounding biased this finding since in our analysis increasing TE risk was only found to be a risk factor for total bleeding in univariable analyses. An unexpected, novel finding is that dental

treatment inflicts a very high bleeding risk on patients. Most dental treatments do not warrant bridging therapy; instead, VKA continuation in combination with the oral administration of antifibrinolytic agents such as tranexamic acid is advised.[22] Several studies report that restarting LMWH in close proximity to the intervention might induce bleeding.[16,17] Our study does not support these findings; the observed high rate (28.8%) of missing values concerning this variable might have diluted this effect.

Strengths and limitations of study

Our study has some weaknesses; the sample size was small and data were analysed retrospectively. We were unable to compare different institutions with respect to guideline adherence, so only a local view on bridging practices could be provided. The strengths of our study are: a well-defined study population and the observational design that allowed us to establish guideline adherence and identify risk factors for bleeding. We allow comparison of our results with other studies because we reported according to the recommendations for reporting studies in periprocedural antithrombotic and bridging therapy, issued by the ISTH.

CONCLUSIONS

Guideline adherence in bridging therapy is poor in the observed single regional setting. This results in patients being unnecessarily exposed to LMWH and for too long periods of time. Since bridging is in general associated with increased bleeding risks,[20,32] it should be avoided in the absence of a good indication. The additional omission of risk stratification based on assessment of renal function further increased bleeding rates. Although these observations are confined to a limited region within one country, there is no reason to expect that this represents a unique and regional problem. Rather, it illustrates the importance of adhering to guidelines for antithrombotic management.

Disclosure

The data were presented at ISTH congress, Amsterdam, the Netherlands on 1 July 2013: poster presentation.

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Comorbidity and treatment decision-making in elderly non-Hodgkin's lymphoma patients: a survey among haematologists

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ABSTRACT

Background: Elderly patients with non-Hodgkin's lymphoma (NHL) are often not treated with standard immunochemotherapy and this might have a negative impact on their survival. Little is known about the determinants that play a role in treatment decision-making of clinicians regarding elderly patients with NHL. The objective of this study was to gain more insight into these determinants.

Methods: A survey was conducted amongst haematologists in the Netherlands. The survey contained questions about comorbidity, polypharmacy, social setting, nutritional status, depression, mild cognitive impairment, dementia, activities of daily living (ADL) and instrumental activities of daily living (IADL) in relation to treatment decisions in elderly NHL patients.

Results: Of all comorbidities, respondents designated cognitive disorders and cardiovascular comorbidity as the most important factors when assessing whether an older patient with NHL is eligible for curative treatment. Also in decreasing degree of importance ADL, IADL and depressive disorder are frequently included in treatment decision-making. Almost half of the respondents feel that treatment of the elderly person is complicated as a result of a lack of scientific evidence.

Conclusion: Haematologists are aware of coexisting problems in elderly patients and they frequently take comorbidities, cognitive disorders and functional status into consideration in treatment decision-making. Future studies are needed to determine the exact role that these factors should play in the treatment of elderly patients. Furthermore, haematologists feel that treatment of the elderly is complicated and there is a lack of scientific evidence, and therefore older adults should be better represented in clinical trials.

KEYWORDS

Comorbidity, elderly, non-Hodgkin's lymphoma, survey.

INTRODUCTION

In 2007, 1572 patients were diagnosed with aggressive non-Hodgkin's lymphoma (NHL) in the Netherlands and it is expected that the incidence will increase to almost 1900 patients in the year 2020 due to ageing of the population and increasing incidence with advancing age.[1] Currently, the median age at diagnosis is 66 years.[2]

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive NHL. The first choice of treatment for DLBCL is the rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) regimen. This improves complete remission rates and survival, in young as well as in elderly patients.[3-12] However, treatment of elderly patients with aggressive NHL can be complicated because of additional factors such as comorbidity and polypharmacy. Furthermore, elderly patients are often under-represented in clinical trials and only relatively fit elderly patients are included. Therefore

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most evidence is based on a selection of patients.[13,14] There are only a limited number of population-based studies with unselected elderly DLCBL patients. These also show that R-CHOP is associated with improved survival in comparison with other treatment strategies.[9,12,15]
Nevertheless, elderly NHL patients are often not being treated with standard immunochemotherapy.[5-8,10,15] Motives for suboptimal treatment are amongst others poor performance status and comorbidity, but also high age in itself is declared by physicians to be a reason for refraining from optimal treatment.[5-8,15]
Little is known about the determinants that might play a role in the decision-making of clinicians regarding the eligibility of elderly patients with a haematological malignancy to be treated with curative intent. Therefore, we conducted a survey among haematologists in the Netherlands to gain insight into these determinants. The emphasis was on DLBCL, as this type of aggressive NHL can be treated with curative intent.

METHODS

Data collection

Haematologists were invited to complete the online questionnaire 'Treatment of the elderly with a haematological malignancy' on behalf of the Dutch-Belgian Cooperative Trial Group for Haemato-Oncology (HOVON). HOVON is a foundation that focuses on improving and promoting treatment methods for adult patients with malignant haematological disorders.[16] Haematologists were invited to participate through e-mail in November 2011. Non-respondents were sent a reminder e-mail within two months.

Study measures

The questionnaire contained questions about the importance of various factors that might play a role in the decision-making of clinicians regarding treatment with curative intent in elderly patients. There were nine questions regarding the extent to which respondents agree that various comorbidities, polypharmacy, social setting and nutritional status should be taken into consideration. In addition, there were five items regarding the frequency with which depression, mild cognitive impairment, dementia, activities of daily living (ADL) and instrumental activities of daily living (IADL) are taken into account. The application of chemotherapy dose reductions in advance and refraining from curative treatment in relation to toxicity was assessed. Furthermore, the respondents were asked to what extent they feel that treatment of older adults with haematological malignancies is complicated because of a lack of scientific research and to what extent respondents exclusively treat elderly patients if they can be included in clinical trials.
Also the respondents' age and gender were assessed, as well as the type of hospital they work in. In the Netherlands, three types of hospitals can be discerned: university hospitals, tertiary medical teaching hospitals (STZ) and general hospitals. STZ hospitals are large teaching hospitals, where highly specialised care is provided.[17]

RESULTS

Invitations to complete the questionnaire were sent to 255 haematologists. A total of 94 questionnaires were returned (36.9% response rate), of which 87 were fully completed and seven were incomplete (*table 1*). The mean age of the respondents at the time of survey was 49.6 years. There were more male than female respondents. Of the respondents, 29.8% worked at a university hospital, 33.0% at an STZ hospital and 37.2% at a general hospital.
The two comorbidities that respondents designated as most important when assessing if an elderly patient qualifies for a curative treatment intent (answer categories totally agree and agree combined) were cognitive disorders (99%) and cardiovascular comorbidity (95.7%) *(figure 1)*. These were followed by pulmonary comorbidity (88.3%), nutritional status (84.1%), social setting (79.8%), kidney disease (70.2), mobility disorders (61.7%), liver disease (57.4%), and polypharmacy (57.4%).
Respondents frequently include dementia (89%, answer categories always and often combined) and ADL (85.7%) in treatment decision-making in elderly patients with a haematological malignancy. IADL (69.4%), depressive disorder (53.2%) and mild cognitive impairment (41.3%) are less often taken into account *(figure 2)*.
Twenty-three percent of the respondents often apply dose reductions in elderly patients to avoid estimated toxicity, while only 2.3% of respondents regularly refrain from treatment with curative intent for toxicity reasons (answer category 'Always' and 'Frequently' combined) *(table 2)*. Of

Table 1. *Sociodemographic characteristics of questionnaire respondents*

	Respondents n=94 n (%)
Age at time of survey (mean ± SD) (N=65)	49.6 (9.0)
Gender	
Male	62 (66.0)
Female	32 (34.0)
Type of hospital	
University hospital	28 (29.8)
Tertiary medical teaching hospital	31 (33.0)
General hospital	35 (37.2)

Figure 1. *Extent to which haematologists agree that various determinants should be included in treatment decision-making in elderly patients with a haematological malignancy*

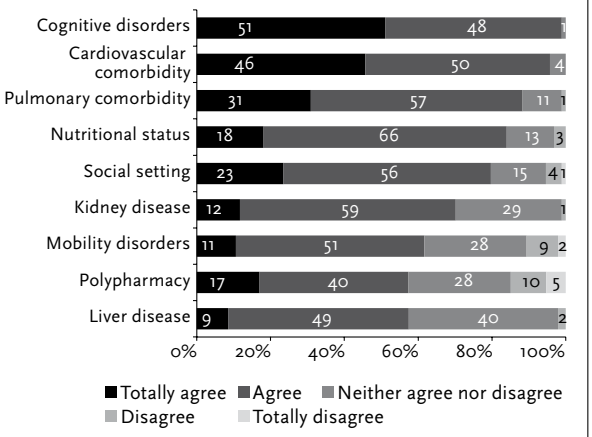
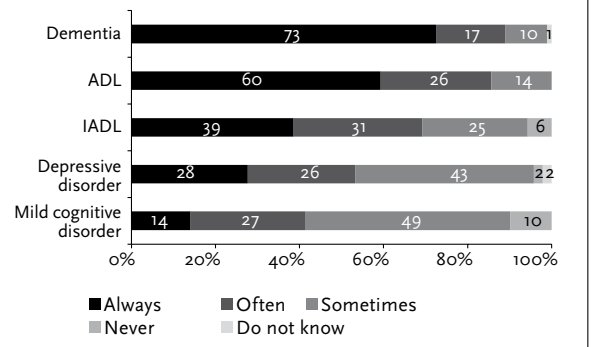


Figure 2. *Frequencies with which respondents include dementia, ADL, IADL, depressive disorder and mild cognitive impairment in treatment decision-making in elderly patients with a haematological malignancy*



the respondents, 45.9% feel that treatment of the elderly is often hindered because there is too little scientific evidence. A minority of respondents (10.3%) only treat elderly patients if they can be included in clinical trials.

DISCUSSION

The aim of the present study was to better understand the determinants that play a role in the decision-making of clinicians regarding treatment with curative intent of elderly patients with aggressive NHL.

Since the incidence of NHL increases with age, comorbidity is common in this patient population and the prevalence of comorbidity ranges from 35 to 79% in elderly NHL patients.[18-22] Our study shows that haematologists are aware of this problem and that they frequently take comorbidity into consideration in treatment decisions.

We observed that, in relation to comorbidity, haematologists found cognitive disorders and cardiovascular comorbidity the most important factors in treatment decision-making. Of the cognitive disorders, in particular dementia is often included in treatment decision-making and to a lesser extent mild cognitive impairment. In addition, respondents stated that they regularly take account of ADL, IADL and depressive disorders.

Several studies demonstrate an interrelationship between the presence of comorbidity and poorer complete remission rates, progression-free survival and overall survival.[10,18-21,23] Nevertheless, it is also observed that in the presence of comorbidity chemotherapy is less frequently applied or that the relative dose intensity is lower.[19,20,22] This suboptimal therapy could also be an explanation for the poorer survival in the presence of comorbidity rather than comorbidity itself. On the other hand, however, there are also studies showing poorer survival in patients with comorbidity, where no relationship was found between comorbidity and chemotherapy dose reductions.[10,21] With regard to cardiovascular comorbidity in particular, there are indications that in the presence of this the chance of

Table 2. *Haematologists' responses to questions regarding dose adjustments and toxicity, lack of scientific evidence and treatment in clinical trials in elderly patients with a haematological malignancy*

	Always N (%)	Frequently N (%)	Sometimes N (%)	Never N (%)	Do not know N (%)
I apply dose reductions in advance in elderly patients because of expected toxicity	4 (4.6)	16 (18.4)	51 (58.6)	16 (18.4)	0 (0.0)
I refrain from curative treatment in elderly patients because of expected toxicity	0 (0.0)	2 (2.3)	69 (79.3)	16 (18.4)	0 (0.0)
I feel treatment decision-making in elderly patients is complicated because there is a lack of scientific evidence	7 (8.0)	33 (37.9)	36 (41.4)	11 (12.6)	0 (0.0)
I treat elderly patients exclusively in clinical trials	0 (0.0)	9 (10.3)	51 (58.6)	20 (23.0)	7 (8.0)

being treated with chemotherapy is reduced and the risk of toxicity is increased.[21] And lastly, in various studies a relation was observed between survival and nutritional status, cognition, frailty, IADL, ADL and depression, but this could not be confirmed in other studies.[23-28] As a result of these inconsistent study results, the interpretation of coexisting diseases in elderly patients with regard to treatment consequences is complicated and more research in this field is necessary.

Interestingly, respondents state that they regularly take comorbidities, cognitive disorders, the patients' social setting, nutritional status, ADL, IADL and depression into consideration when making treatment decisions. However, in daily clinical practice systematic assessments are rarely carried out to identify problems in these areas; this is, among other reasons, because it is time consuming. In general, the physicians' judgment is used to estimate whether there are additional problems, even though it is known that this is not very reliable. Comprehensive assessment results in the detection of a higher number of previously unknown geriatric problems than the physicians' judgment, although it is still not known how to adjust treatment decisions based on comprehensive geriatric assessments.[29-33]

Finally, a large proportion of the respondents feel that treatment of the elderly is difficult, because relatively little scientific research has been done among this population. Indeed, older adults are poorly represented in clinical trials, due to direct age-based exclusion as well as due to restrictive inclusion criteria, selecting for the fittest elderly.[13,14] Since the majority of all DLBCL patients are elderly, it is important that they are better represented in randomised controlled trials so that treatment of this population can be improved.

The current study has some limitations. We did not define the term 'elderly patient', but left this to the interpretation of the respondent. Furthermore, we cannot exclude that haematologists with a special interest for elderly patients with NHL responded. However, there are no direct indications for this.

The strengths of our study are that this is, to the best of our knowledge, the first study investigating the determinants that influence treatment decision-making. In addition, it is a multicentre study including haematologists from university hospitals as well as STZ hospitals and general hospitals and the participation rate of the haematologists was high. Therefore we are confident that the results of our study are generalisable.

In conclusion, haematologists are well aware of coexisting problems in elderly patients and comorbidities, cognitive disorders and functional status are frequently included in treatment decisions. There is, however, no convincing evidence of the exact role comorbidity should play in the treatment of elderly NHL patients. Moreover, clinicians feel that treatment is complicated due to a lack of scientific evidence. Therefore, future studies should address this problem and older adults should be better represented in clinical trials, so that evidence-based guidelines for the treatment of elderly patients with a haematological malignancy can be developed.

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W.J. Mulder has declared no conflict of interests.

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SPECIAL ARTICLE

Antibiotic treatment of moderate-severe community-acquired pneumonia: design and rationale of a multicentre cluster-randomised cross-over trial

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ABSTRACT

Background: For the empirical treatment of community-acquired pneumonia requiring admission to a non-ICU ward, the Dutch guidelines recommend either beta-lactam monotherapy, beta-lactam and macrolide combination therapy, or fluoroquinolone monotherapy. The lack of convincing evidence to preferentially recommend any of the three empiric regimens results from intrinsic limitations of current studies, such as bias by indication and residual confounding in observational studies, and the unknown effects of pre-randomisation antibiotic use in randomised controlled trials. In this paper we discuss the methodological drawbacks of observational cohorts and randomised controlled trials in antibiotic therapy. Next, we explain why we designed a multicentre cluster-randomised cross-over study to evaluate the effectiveness of three antibiotic treatment strategies, consisting of a preferred treatment regimen of beta-lactam monotherapy, beta-lactam and macrolide combination therapy or fluoroquinolone monotherapy, in adult patients admitted to a non-ICU ward with a clinical diagnosis of community-acquired pneumonia. Furthermore we outline different aspects of this design that deserve thorough consideration.

Conclusion: We discuss different aspects of a cluster-randomised cross-over trial that is designed to determine the effects of three recommended regimens of antibiotic treatment of CAP.

KEYWORDS

Antibiotic therapy, cluster randomisation, community-acquired pneumonia, study design, trial

INTRODUCTION

Community-acquired pneumonia (CAP) has an incidence ranging from 3.3-46 per 1000 per year in the elderly population.[1-4] Reported case fatality rates are usually less than 5% in outpatients, but hospital mortality rates have ranged from 5-48%, depending on age, comorbidities, pneumonia severity and presence of bacteraemia.[2]

With the introduction of sulphonamides and penicillins in the 1930s, the estimated absolute risk of dying from CAP decreased by 10-25% for all CAP patients, and even by 48-65% in bacteraemic CAP patients. Yet exact estimates are difficult to derive since randomised placebo-controlled trials (RCTs) have not been performed.[5] Advances in medical care, such as mechanical ventilation and vasopressor support, have most certainly improved survival in patients with high severity CAP, but for the majority of CAP patients, major improvements in the management of CAP are less obvious.[6] Adjunctive treatment with immunomodulators, e.g. corticosteroids, have not demonstrated clear improvements in survival.[7] Therefore, antimicrobial therapy remains the mainstay of CAP treatment.

Initial antibiotic therapy for CAP is usually empirical, covering the most frequent pathogens. Yet, patient and disease characteristics are not specific enough to guide antibiotic therapy in most patients.[8,9] Therefore, CAP severity, as determined by prognostic scores or site of admission, is widely recommended for guiding empiric antibiotic therapy.[8-11] In the Netherlands, it is recommended to treat patients with mild CAP empirically with doxycycline or amoxicillin, and those with severe CAP with combined treatment of a beta-lactam (such as second- and third-generation cephalosporins) and a macrolide,

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or a beta-lactam (such as penicillin or amoxicillin) and ciprofloxacin, or monotherapy with one of the newer fluoroquinolones (moxifloxacin or levofloxacin). The mid-range severity group, labelled moderate-severe CAP, should be treated either as mild CAP or as severe CAP, based on the perceived risk of *Legionella* infection. Three different classification tools are recommended to categorise CAP severity, with the recommendation to consistently use one of them: CURB-65 (0-1 is mild, 2 is moderate-severe and >2 is severe), PSI (1-2 is mild, 3-4 is moderate severe and 5 is severe), or a pragmatic score based on the level of care needed (ambulant is mild, non-ICU ward is moderate-severe, ICU admission is severe).[9] Because of the multiple options for severity classification and the subjectivity of clinical parameters, the use of these scoring systems promotes categorisation of patients as severe CAP, with corresponding treatment choices. This becomes apparent in different studies of moderate-severe CAP, in which 20-40% of patients were treated with quinolones or combination therapy with a macrolide.[12-15] Recently, our group has investigated guideline adherence in hospitalised CAP patients in the Netherlands, and reported very heterogeneous empirical treatments.[16] In the Netherlands the three recommended empirical regimens are considered equivalent for moderate-severe CAP. In the international literature, the discussion concerning the need for atypical coverage in non-ICU hospitalised CAP is still ongoing.[17-20] Each strategy comes with different advantages and drawbacks. Beta-lactam antibiotics have less adverse events than macrolides, are less expensive than fluoroquinolones and the prevalence of antibiotic resistance in *Streptococcus pneumonia* is not clinically relevant in the Netherlands.[21,22] Yet, atypical pathogens are not covered. Macrolides are active against most atypical pathogens and they might offer anti-inflammatory effects, possibly leading to faster clinical responses.[23] On the other hand, rapid development of resistance of *S. pneumoniae* against macrolides during treatment has been observed in vivo.[24] In the Netherlands, proportions of *S. pneumoniae* isolates from hospitalised patients that were resistant to macrolides were 2-3% in 1996, 7-10% in 2002 and 4.5% in 2011.[21,22] The newer fluoroquinolones, such as levofloxacin and moxifloxacin, are active against all common causes of CAP, can be used intravenously and orally, and might also have anti-inflammatory effects.[25] The major disadvantage, similar to macrolides, is a potentially higher risk of development of antibiotic resistance, as observed among *S. pneumoniae* after introduction of fluoroquinolones in Canada and Hong Kong.[26,27] In contrast, a study from Germany showed a low prevalence of quinolone resistance, while usage of moxifloxacin was high.[28]

The lack of well-designed randomised comparisons between beta-lactam monotherapy, beta-lactam and macrolide combination therapy and any of the newer fluoroquinolones is a serious limitation for interpreting the relative effectiveness of these strategies in patients hospitalised with CAP. Fluoroquinolones have been compared with beta-lactams and macrolides in randomised studies, but none yielded superiority of either treatment. Large meta-analyses failed to demonstrate an advantage of atypical coverage in the empirical antibiotic treatment of mild to moderately severe CAP patients not caused by *Legionella*.[29-31] Some observational studies showed beneficial effects of atypical coverage on clinical outcome,[32-40] but in a similar number of studies such effects could not be demonstrated.[41-49]

However, there are serious limitations in the design of observational studies and RCTs. To overcome some of the pitfalls of these classical study designs, we designed the 'Community-Acquired Pneumonia – Study on the initial Treatment with Antibiotics of lower Respiratory Tract infections' (CAP-START, http://clinicaltrials.gov/show/NCT01660204), a cluster-randomised cross-over study to evaluate the (cost-)effectiveness of three empirical antibiotic strategies in patients hospitalised with CAP in non-ICU wards. The first aim of this paper is to discuss the pros and cons of observational studies and RCTs. Next, we discuss different aspects of designing a cluster-randomised cross-over study, which we consider beneficial for the development of future trials for the comparison of intervention strategies.

DRAWBACKS OF OBSERVATIONAL STUDIES FOR ANTIBIOTIC TREATMENT OF CAP

In observational studies, the decision for empirical antibiotic treatment was made by treating physicians. Consequently, these studies suffer from bias by indication, as the choice of therapy will be influenced by e.g. severity of disease or the patients' overall prognosis. Thus, if patients receiving atypical coverage have a better outcome, this may in part result from the better prognosis at baseline, and not necessarily from better coverage of atypical pathogens. The magnitude of this form of bias was demonstrated by using a propensity score to predict treatment allocation based on clinical variables. The propensity was used in a multivariate analysis to adjust for confounding variables. The apparent beneficial effect of combination therapy (adjusted OR 0.39, 95% CI 0.19-0.79) was diminished after additional correction for the propensity score (OR 0.69, 95% CI 0.32-1.48).[50] Although analytical control in multivariable analysis is usually attempted, many determinants may be unknown or measured with error, resulting in residual confounding. For example, (hidden) treatment restrictions may play a role in a substantial proportion of fatal CAP cases,

especially in elderly patients with severe comorbidities,[51] which may also influence treatment decisions and, thus, confound observations. It is difficult, if at all possible, to predict the direction and quantity of residual confounding.

DRAWBACKS OF RANDOMISED CLINICAL TRIALS FOR ANTIBIOTIC TREATMENT OF CAP

Randomisation prevents bias by indication and residual confounding because treatment allocation is not influenced by patient or disease characteristics, but determined by chance. However, a consequence of an RCT is that the timeframe for initiation of the study medication is generally longer than in clinical practice, because the informed consent procedure and randomisation need to be realised. International guidelines for clinical trials demand that eligible subjects are given sufficient time to consider participation in the trial. At the other end, current CAP guidelines emphasise the importance of early antibiotic administration, and recommend initiation of treatment within four to eight hours of hospital admission.[8,9,52] As a result, many patients have already received in-hospital antibiotic treatment before study enrolment. Since the adequacy of the first dose of antibiotics is considered crucial for patient outcome,[53-55] this may severely compromise accurate evaluation of effectiveness of the randomised antibiotics. In fact, it might even be dangerous to accept non-inferiority if a large proportion of patients has received similar pre-randomisation antibiotics. Any difference in effectiveness will, to some extent, be diluted by the therapeutic effect of the antibiotics received prior to randomisation, leading to a reduced power to detect superiority of one of the antibiotics under study.

Another limitation of current RCTs is that their generalisability to daily clinical care is questionable. Prior antibiotic use, contraindications, and exclusion criteria can lead to a very restricted study population. A comparison of empirical antibiotic strategies, in which the aforementioned exclusion criteria are not applied, would lead to more generalisable results.

CLUSTER-RANDOMISED CROSS-OVER DESIGN

In an ideal comparison of empirical antibiotic therapies, the allocation of treatment would be unrelated to patient and disease characteristics, to ensure comparability of the treatment groups in terms of prognosis. Additionally, the timing of treatment and of concomitant therapy should be comparable with clinical practice. As pointed out, when studying empirical antibiotic treatment of CAP, the first requirement is not satisfied in observational studies, while RCTs do not comply with the second. Also, patients should be included on an intention-to-treat basis; treating physicians should be able to start another antibiotic because of prior use or contraindications. To overcome these limitations, we have designed a multi-centre cluster-randomised cross-over study, comparing empirical antibiotic strategies. Participating centres are randomised to three consecutive periods of four months, in which one of the three empirical antibiotic strategies applies. All CAP patients admitted to a non-ICU ward, irrespective of the PSI or CURB-65 classification, are eligible for the study. The empirical strategies consist of beta-lactam monotherapy, fluoroquinolone monotherapy and beta-lactam macrolide combination therapy.

In this way, allocation of empirical strategy is determined by the date of admission and cannot be biased by patient characteristics. In each hospital the local antibiotics committee has been asked to adopt this empirical strategy as the standard treatment for CAP during that period. Because of this, the medical ethics review board judged that this cluster-randomised study is not liable to the same regulations as an individually randomised trial. Consequently, written informed consent is not needed prior to the start of the preferred treatment of the study, but only for collection of individual patient data. Importantly, this is only legitimate for interventions that are registered for the disease under study and are considered equally effective.

Treating physicians will sometimes deviate from this strategy for medical reasons. These patients will also be included in the intention-to-treat analysis, which will be the primary analysis of our study. Thus, the strength of a cluster-randomised trial design is that it enables a comparison of treatment strategies, rather than the individual treatments. Since patients from one hospital may not be comparable with those from another hospital, the cross-over design is used, enabling adjustment for hospital-specific confounding factors.

The most important challenges with this design include adherence to the treatment strategy by the treating physicians, prevention of selection bias, and differences in number and severity of eligible CAP patients due to seasonality. These will be discussed in the next section.

CHALLENGES IN CLUSTER-RANDOMISED CROSS-OVER TRIALS FOR ANTIBIOTIC TREATMENT OF CAP

Protocol adherence and route of administration

Naturally, treating physicians sometimes deviate from study protocols. This may compromise the intention-to-treat analysis if the alternative antibiotic therapy is

different in effectiveness. If, however, the rationale for deviation from protocol is valid, i.e. in line with common practice, the intention-to-treat analysis will show the effect of implementation of either protocol in real life. Therefore, reasons for such deviations will be recorded to investigate their validity. Valid reasons include failure of prior antibiotic treatment with the same class of antibiotics, clinical suspicion of a pathogen that is not covered by the preferred regimen, targeted treatment because of previous microbiological results or a contraindication for the treatment of choice. Episodes of non-protocol adherent treatment without a valid medical reason are considered protocol violations. All CAP patients, including those with protocol deviations and protocol violations, will be included in the intention-to-treat analysis. Hence, in this analysis we compare hospital-wide strategies of empirical treatment rather than antibiotics in individual patients. For instance, patients receiving non-preferred antibiotics for medical reasons are still treated according to best medical practice during that study period. Rates of protocol deviations will provide insight into the implementation potential of each treatment strategy. In a classical RCT, such patients would be excluded because of a contraindication for one of the treatment options. On the other hand, the per-protocol analysis will only include patients treated according to the preferred antibiotic regimen. Reasons for non-adherence will probably differ between treatment arms, and protocol deviations may therefore confound the per-protocol analysis if the protocol adherent patients in one period have a different prognosis compared with those in another. This will be dealt with in the statistical analysis.

The specific choice of agents within the treatment category is left to the treating physician, e.g. amoxicillin, co-amoxiclav or ceftriaxone are all acceptable as beta-lactam monotherapy. All changes in therapy are monitored and deviations from protocol will be motivated by the treating physician. Although this approach will lead to a heterogeneously treated study population, and the antimicrobial activity of different agents within one class may differ, we have assumed that, in the empirical treatment of CAP, such differences are negligible compared with the additional coverage of atypical agents (by macrolides or fluoroquinolones) or the immunomodulatory effects of macrolides. Furthermore, the primary goal of this study is to compare treatment strategies rather than individual antibiotics. Decisions on the route of administration (intravenous or oral), the duration of antibiotic treatment, and the start of pathogen-directed therapy when a causative agent has been identified, will be taken according to the Dutch CAP guidelines.[9]

Improving compliance to the protocol

Sub-optimal adherence to study protocol is a threat to any study. As most CAP patients receive their first antibiotic dose in the emergency room (ER), all pulmonary, internal and ER physicians, and especially the residents, need to be informed about the study. In some hospitals this comprises a group of over 50 people with multiple changes due to rotations, career choices, holidays and leaves. We designed a three-step approach to optimise study protocol adherence. First, all physicians were informed through presentations at the start of the study, and presentations are repeated regularly. Second, study progress was communicated through monthly (and later two-monthly) newsletters. Third, adherence to study protocol was continuously monitored and proportions of patients classified as 'adherent', 'deviation with clinical reason' and 'protocol violation' are regularly fed back to participating sites.

The intensity of information provided to physicians working 'in the field' is challenging, as in our experience there is a subtle balance between the level of knowledge required for such a trial and the risk of information fatigue. The return of investment of informative group sessions was considered limited as the awareness of the study seemed to decrease rapidly after such meetings. They are necessary at the start of the study, after which individual contacts, both through key persons in each hospital and directly with the care-providing physicians, are more essential for optimising protocol compliance.[56,57] We, therefore, monitor compliance case by case directly after study inclusion, and ask the physician who initiated the treatment for the rationale of any deviation from study protocol that is not motivated in the patient records. Initially, we experienced some resistance to this approach, as it was perceived as criticism on treatment decisions by some. However, after explaining the reason, all understood and accepted this procedure. Along the way, an increasing number of physicians explicitly reported the rationale for deviations in the medical records.

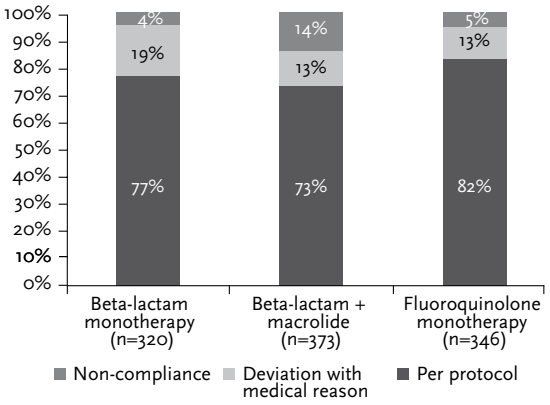
Naturally, providing adequate information to caregivers is very important around the four-monthly switches of the preferred regimen to another antibiotic class. In our experience it takes one to two weeks to facilitate a change to the new standard treatment. As a consequence there are more protocol violations at the beginning of each cluster. In future studies using a similar design, investigators might consider the use of a run-in period, in which subjects are not included in the study while the interventional change is effectuated.

Figure 1 provides an example of how we reported the protocol compliance to the participating centres. Treatment according to protocol was highest during the fluoroquinolone period, and lowest during the periods of beta-lactam plus macrolide therapy.

Subject recruitment

A potential pitfall of a cluster-randomised study is patient inclusion with knowledge of treatment allocation. This

Figure 1. *Compliance to the protocol for the first 1039 patients*



may induce bias if inclusion criteria are not applied uniformly across different treatment arms.[58] Therefore, it is important to have clear inclusion criteria that are easily applicable. In CAP research the presence of an infiltrate on the chest X-ray is often used as one of the inclusion criteria. However, interpretation of the chest X-ray is not unambiguous and inter-observer agreement is therefore moderate.[59-61] Also, appearance of an infiltrate is delayed in a proportion of CAP patients.[62] Subsequent chest X-rays are mostly performed because of treatment failure, and will reveal an infiltrate in a proportion of the patients with initially negative chest radiographs. Therefore, if patients were to be included based on presence of an infiltrate, this could lead to selection bias. In addition to that, the domain of interest of this study does not consist of patients with proven CAP, but of patients who are treated for CAP, regardless of the presence of an infiltrate. Hence, inclusion in our study is based on a working diagnosis of CAP. We intend to perform a sensitivity analysis of patients with proven CAP. Definitions of CAP are very diverse in the literature (for example, Oosterheert et al., Snijders et al. and Ewig et al.[13,15,44]). We used a combination of several clinical parameters and a working diagnosis of CAP documented by the treating physician, as detailed in box 1. Screening for eligible patients is performed daily by research nurses not involved in the treatment of patients and is based on the admission diagnosis in the medical charts. Written informed consent, for the purpose of individual patient data collection, is requested by the research nurse or the treating physician. Of all eligible patients who are not included, the admission date and reason for non-inclusion is recorded, so that inclusion practice can be compared between hospitals and between treatment arms. We expect that the most important reason for non-inclusion will be patient refusal. Logistical reasons, such as discharge before the patient has been approached for inclusion, and ethical reasons, such as a presumed undue burden to the patient, should be closely monitored to ensure that these are not different between treatment arms. Selective recruitment, if present, will become apparent in differences in the inclusion rate or in differences in CAP severity between treatment arms. The magnitude of this will be assessed analytically, which is discussed in the section on data analysis.

Measurement of outcomes

As optimal treatment may require protocol deviation, blinding for treatment is not feasible. Therefore, it is pivotal to have an unambiguous study endpoint, preventing any bias in this aspect.[63,64] The primary endpoint is all-cause mortality up to 90 days after hospital admission with CAP, which can be obtained even if a patient's status at day 90 is not available in the hospital records (i.e. no death recorded and patient is not seen alive after day 90) from the Municipal Personal Records Database. Secondary outcomes include the length of intravenous treatment, length of hospital stay, complications relating to pneumonia or treatment, time to return to work and usual activities and (non) healthcare costs. Length of stay and length of intravenous treatment can be measured accurately, but may be more prone to bias because of the open label design. Self-reported time to return to usual activities and non-healthcare costs will probably not be influenced by knowledge of the type of antibiotic received, as most patients will not be aware of the pharmacological properties of their antibiotics.

Seasonality

Because of the seasonality of CAP, numbers of eligible patients will change over the year, which may also be the case for the average severity of CAP and spectrum of pathogens. In RCTs, this does not have consequences, since patients are randomised individually, and treatment arms will consist of comparable patients. However, in cluster-randomised cross-over trials, seasonality poses a challenge, because, by design, patients in one cluster are in a different season compared with those in another cluster. This may lead to an unequal number of inclusions between arms, which is less efficient for the analysis. More important, if the severity of CAP differs between seasons, this would lead to a biased evaluation. Although no evidence exists that CAP severity differs between seasons, aetiology is known to show variation.[65] Therefore, we aimed for a wedged start of periods to ensure continuous inclusion of patients across the year in all treatment arms.

Unfortunately, as the trial was initiated at different time points due to logistical reasons in some of the participating

hospitals, the wedged start of periods was suboptimal. As a result, there are several months in the course of the study in which a substantial proportion of inclusions are made in one specific treatment arm. We are therefore planning to confirm analytically whether seasonality is of influence for the relative treatment effect. Furthermore we aim to compare proportions of pathogens between the treatment arms. For future studies with a cluster-randomised cross-over design, in which seasonality may play a role, we recommend to randomise based on calendar month. For example, assuming three periods of four months each, if the randomisation scheme of all centres is to start in January, and one centre, randomised to treatment order A-C-B, starts in July, it will start with two months of C, next have 4 months of B and 4 of A, and finish with two other months of C. Alternatively, if feasible, periods of one year could be chosen to avoid seasonality effects.

Sample size calculation

The study is designed to demonstrate non-inferiority of beta-lactam monotherapy on 90-day mortality. Based on an expected mortality rate of 5%,[14] 650 patients per study arm are needed to demonstrate non-inferiority to either strategy with a non-inferiority margin of 3% (alpha of 0.05 and power of 0.80). Accounting for possible drop-outs, 700 patients need to be included in each study arm. Based on expected numbers of patients in each centre, a total study period of 24 months (6 periods of preferred antibiotic regimens) in seven participating centres was deemed necessary. In classical cluster-randomised studies, the statistical power is generally reduced because of the intra-cluster correlation and because cluster sizes are unequal. The cross-over design limits these cluster level effects.[66] Furthermore, the effects of intra-cluster and inter-period correlation are considered limited, since treatment of one patient does not affect outcome of other patients, and clinical outcomes are associated with a low inter-cluster and intra-cluster correlation in general.[67] We performed a power simulation, comparing a classical RCT design with the cluster-randomised cross-over design, and estimated that statistical power is reduced in the latter by only 0.5% (95% confidence interval: 0.2 to 0.8%; simulation script is available on request to the authors).

Data analysis

Analysis will be performed according to the CONSORT statement recommendations for cluster randomised trials.[68] Since complexity and disease severity of patients might differ between hospitals, multilevel analysis will be used. The effect on the primary endpoint, 90-day all-cause mortality, will be determined by a random-effects logistic regression model. Both intention-to-treat and per-protocol analyses are planned, and stratified analyses are planned for severe CAP and non-severe CAP according to CURB-65 and PSI scores. The effect on length of hospitalisation and length of intravenous treatment will be determined by a random-effects cox regression model. Alternative approaches to the analysis of cluster-randomised trials have been proposed, including cluster-level analysis and hierarchical models, which are discussed elsewhere.[69]

Another consideration in cluster-randomised cross-over trials, similar to individual patient cross-over trials, is what is known as the carry-over effect: the effect of treatment in one period may continue to have an effect in the next period. If so, a wash-out period should be implemented, which should be sufficiently long to eliminate the carry-over effect. Further testing for and analytical control of carry-over effects is debatable, since the power to find a carry-over effect is often limited.[70] Since in our trial the treatment of one patient does not affect the outcome of others, carry-over effects will not be present. Therefore, no wash-out period is used and the analysis will not take carry-over effects into account.

As mentioned before, different mechanisms may lead to incomparability of the treatment groups. Therefore, analytical control of potential confounders is deemed necessary in cluster-randomised trials. Unlike in observational studies, selection of potential confounders is not based on an expected association with treatment allocation, because this association, if present, will be the result of mere chance in a cluster-randomised trial. For this reason, all analyses will be adjusted for known prognostic factors of the outcome. For example for mortality, these include age, gender, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment, PSI score, prior admissions in the past year and receipt of immunosuppressive therapy.

Potential applications of this study design

A cluster-randomised cross-over trial could be suitable in other areas of acute care medicine. When study treatment has to be started within a short period of time, and cannot be delayed by study procedures, this design may be superior to an RCT. Examples would include any severe infection requiring antimicrobial therapy, comparisons of biomarker-guided treatment decisions on the ER, treatment of acute myocardial infarction or stroke, and others. Importantly, the study treatments should be considered equally effective, and they should therefore be registered treatment options.

Summary

This study aims to determine the (cost)-effectiveness of three recommended strategies for empirical treatment of patients with a working diagnosis of CAP admitted to a non-ICU ward. The three strategies are beta-lactam monotherapy, fluoroquinolone monotherapy and combination therapy of a beta-lactam and a macrolide.

Box 1. *Study definitions*

Community-acquired:

Defined as an infection occurring in patients who had not been recently hospitalised (>48 hours in the past two weeks) and not residing in long-term care facilities.

Working diagnosis of CAP:

Defined as presence of at least two of the following clinical criteria* and treated with antibiotics for a clinical suspicion of CAP as documented by the treating physician. Patients with two or more criteria and an obvious non-respiratory source of the infection are not considered a working diagnosis of CAP.

Proven CAP:

Defined as a working diagnosis of CAP, with presence of a new or increased infiltrate on chest X-ray or CT scan and at least two other clinical criteria*.

* *Clinical criteria:*

- Cough
- Production of purulent sputum or a change in the character of sputum
- Temperature >38°C or <36.1°C
- Auscultatory findings consistent with pneumonia including rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
- Leucocytosis (>10 x 10^9 white blood cells/litre or >15% bands),
- C reactive protein more than three times the upper limit of normal
- Dyspnoea/ tachypnoea/ hypoxia
- New or increased infiltrate on chest X-ray or CT scan

The cluster-randomised design of the study overcomes potential effects of confounding by indication and of pre-randomisation antibiotic use. Moreover, since the present study will compare empirical antibiotic strategies and patient inclusion is based on a working diagnosis of CAP, the study results will be generalisable to the patients who are eligible for treatment in clinical practice.

Naturally, deviations from protocol are possible (and will be needed) for medical reasons. All patients will be included in the intention-to-treat analysis, allowing the comparison of the different treatment strategies as they would be implemented in clinical practice. However, true protocol violations (non-adherence without medical reason) are a threat to the study validity, and will, therefore, be monitored closely. Reasons for deviation will be recorded in the final study results and it is aimed to have less than 10% protocol deviations without medical reason.

Another important hazard for the validity of a cluster-randomised trial is differences in inclusion rates across study arms. We minimised this risk by using the clinical diagnosis as inclusion criterion, independent of compliance to the study protocol. Still, any differences in inclusion may lead to bias, which has to be dealt with analytically.

In conclusion, a properly executed cluster-randomised cross-over trial will provide a valid evaluation of empirical antibiotic strategies for patients hospitalised with CAP.

Disclosures

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Trial registration: ClinicalTrials.gov NCT01660204.

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LETTER TO THE EDITOR

Fatal methylene blue associated serotonin toxicity

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ABSTRACT

This is the first report of a fatal outcome from serotonin toxicity, precipitated by an interaction between methylene blue and venlafaxine. Methylene blue-associated serotonin toxicity has been described before but usually as mild toxicity. Its presentation after general anaesthesia may be atypical and therefore more difficult to diagnose. However, the syndrome is completely preventable if serotonin re-uptake inhibiting agents are stopped beforehand.

What was known on this topic ?
Methylene blue has been associated with severe central nervous system toxicity and has subsequently been shown to act as a monoamine oxidase inhibitor and can give rise to serotonin toxicity.

What does this add ?
Methylene blue-associated serotonin toxicity can be fatal and its presentation may be atypical after general anaesthesia.

KEYWORDS

Serotonin toxicity, serotonin syndrome, methylene blue, methylthioninium chloride, 5HT-2A antagonism, hyperthermia, fatal

INTRODUCTION

Methylene blue (methylthioninium chloride) is, among other indications, used in parathyroid surgery to facilitate visualisation of the parathyroid glands.[1] It is administered intravenously shortly before surgery and is quickly absorbed into the pathological tissues with a resulting blue discoloration.
Methylene blue is commonly regarded as an inert dye, but has recently been shown to act as a potent reversible monoamine oxidase (MAO) inhibitor with a strong preference for MAO-A inhibition.[2] Because the inhibition constant is in the nanomolar range, even small doses of methylene blue (less than 1 mg/kg) may exert clinically relevant MAO inhibition.[3] This effect is enhanced because methylene blue is rapidly absorbed in nervous tissue where, in rat models, it reaches brain concentrations ten times higher than in serum.[4]
Therefore, methylene blue can lead to serious side effects. Because MAO inhibition increases the intrasynaptic levels of serotonin (5-HT), serotonin toxicity is to be expected, especially when methylene blue is combined with serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). This report is the first of a fatality precipitated by probable serotonin toxicity, involving methylene blue and a SNRI.

CASE REPORT

A 70-year-old female was diagnosed with primary hyperparathyroidism and scheduled for surgery under general anaesthesia. Her past medical history was significant for diabetes, an ischaemic CVA and a mood disorder for which she used venlafaxine 75 mg twice daily. On the morning of her surgery, the patient took her last dose of venlafaxine and one hour before induction of

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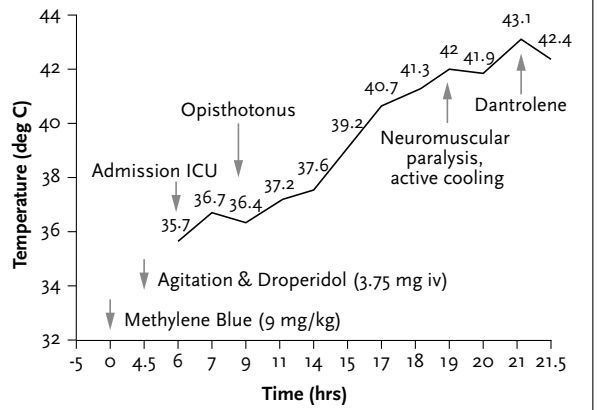
anaesthesia, 1 gram of methylene blue (9 mg/kg) was given intravenously. Anaesthesia was performed with propofol induction and sevoflurane maintenance and atracurium was used for muscle relaxation. After surgery, in the recovery room, the patient suddenly became agitated. Hypoglycaemia was ruled out and symptomatic treatment instituted with droperidol and midazolam. However, her mental status deteriorated for which the neurologist and internist were consulted. The neurological examination showed agitation, reduced consciousness, pupillary dilatation, ocular clonus, dysarthria, neuromuscular hyperactivity and hyperreflexia, predominantly in the lower limbs. The temperature was 36 °C. A relevant hypocalciaemia or hypercalciaemia and a haemorrhagic cerebrovascular accident (CT scan) could be excluded. Because of further neurological deterioration with profuse sweating, hypersalivation, opisthotonus and a bilateral pyramidal syndrome, the patient was transferred to the intensive care unit with a differential diagnosis of malignant neuroleptic syndrome, ischaemic brainstem infarction or epileptic insults with postictal status (for which valproic acid was started). On admission she had normal vital functions but after nine hours her temperature rose to 39 °C *(figure 1)*. The patient became respiratory and haemodynamically unstable and she needed intubation and mechanical ventilation. Cooling was instituted with infusion of 2 litres of cold fluids and application of a fluid filled cooling blanket. Because of worsening hyperthermia, dantrolene (1.8 mg/kg) was given. Maximum temperature was 43.1°C. Although the temperature decreased after dantrolene administration, the patient died from circulatory collapse not responding to volume resuscitation, inotropes and vasopressors. Permission for autopsy was not granted.

Figure 1. *Temperature course*



DISCUSSION

Methylene blue-associated neurotoxicity has been incidentally reported since 2003 and the association with serotonin toxicity was made in 2006. Ramsay showed that methylene blue is a potent MAO-A inhibitor.[2] Low doses of 0.7-1 mg/kg methylene blue intravenously may already give rise to clinically relevant MAO inhibition.[3,5]

Two retrospective surgical series describe postoperative encephalopathy in 17 of 325 patients (5%) after parathyroid surgery with the use of methylene blue.[6,7] All of them used SRI agents. Additionally, 15 cases have been reported with serotonin toxicity during the use of methylene blue.[8,9] Our patient, however, is the first fatality from probable serotonin toxicity described in the literature. We reported the case to the relevant authorities.

Serotonin toxicity or serotonin syndrome consists of a clinical trial of changed mental status, autonomic stimulation and neuromuscular excitation. Mono-intoxication with SRI agents only leads to moderate toxicity (without severe hyperthermia), for severe toxicity concurrent use of a MAO inhibitor is required.[8] Diagnostic criteria have been proposed and the Hunter criteria focus on specific neuromuscular signs in the context of SRI agents, such as a rapid onset, hyperreflexia, tremor and inducible or spontaneous (ocular) clonus, with symptoms often more pronounced in the lower limbs.[10]

Our patient showed most of these discriminating signs, except the rapid onset. This may be explained by her general anaesthesia which, in animals, induces preferential brain hypothermia and therefore may lead to a protracted course and atypical presentation of serotonin toxicity.[11] In our case, clinical symptoms arose 4.5 hours after administration of methylene blue, but hyperthermia was only observed after 15 hours.

Treatment is based on two key points: discontinuation of the implicated drugs and aggressive supportive therapy. Agitation can be controlled with benzodiazepines. Moderate and severe toxicity may benefit from serotonin receptor 2a (5-HT2A) blockade with cyproheptadine tablets or parenteral chlorpromazine most often cited. There are, however, also other potent 5-HT2A antagonists such as olanzapine and ketanserin.[12,13] Ketanserin does have the benefit of intravenous availability and a lack of effect on dopamine receptors which makes it a safer choice if neuroleptic malignant syndrome cannot be excluded.

Hyperthermia should be treated with cooling therapy including sedation and muscle relaxation. The use of dantrolene in hyperthermic syndromes apart from the classical malignant hyperthermia is not well defined. Dantrolene may be of additive value because it modulates not only peripheral muscle ryanodine receptors but also cerebral ryanodine receptors. This modulates the dopaminergic system which may be involved in the

pathogenesis of some centrally mediated hyperthermic syndromes.[14]

In conclusion, serotonin toxicity is a predictable and hence preventable side effect if methylene blue is combined with SRI agents. Routine use in parathyroid surgery is not advised and there are better alternatives available for intraoperative localisation. If methylene blue is applied, stopping SRI agents five half-lives before administration of methylene blue is sufficient to prevent serotonin toxicity. Therefore, a drug withdrawal of two weeks is needed for most SSRIs and of five weeks for fluoxetine.

Because of the wide use of SRI agents, the existence of other indications for methylene blue outside parathyroid surgery *(table 1)* and the unawareness of the diagnosis of serotonin toxicity in general, we think the real prevalence of methylene blue-induced serotonin toxicity is greater than reported and needs clinical attention.

Table 1. *Clinical indications or active recruiting studies with the use of methylene blue*

	Methylene blue dose	ST reported
Methemoglobinaemias	1-2 mg/kg IV	No
Ifosfamide-induced encephalopathy	50 mg IV every four hours till symptoms resolve	Yes[5]
Treatment of vasoplegic syndrome	2 mg/kg IV	No
Parathyroid imaging	3-7.5 mg/kg IV	Yes[6,7]
Treatment of malaria	10 mg/kg twice a day orally for three days	No
Colonic diagnostic staining	200mg orally single gift	No
PTSD treatment adjunct	260 mg orally for 6 days	No

PTSD = post-traumatic stress syndrome; ST = serotonin toxicity.

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